The Chronicle of SKIN & ALLERGY

PRACTICAL THERAPEUTICS *and* CLINICAL NEWS *from the* WORLD *of* DERMATOLOGY ■ FEBRUARY 2014

Research

Small molecules seen as next advance in psoriasis therapy

■ Oral biologic may be helpful for patients reluctant to receive injections

by LOUISE GAGNON,
Correspondent, The Chronicle

The advent of small molecules that are taken orally represent the next revolution in psoriasis therapy, according to Dr. Kenneth Gordon.

"You will see a number of new medications [to treat psoriasis] in the next few years," said Dr. Gordon during a presentation at Dermatology Update 2013 in Montreal.

Discussing phase III results from the ESTEEM 1 (Evaluate Safety and Effectiveness of Oral Apremilast in Patients with Moderate to Severe Plaque Psoriasis) trial, the larger of two randomized, placebo-controlled studies evaluating apremilast, an oral, small molecule that inhibits phosphodiesterase 4, Dr. Gordon noted that laboratory values that have been reported with the use of apremilast suggest that the drug is very safe. He is a clinical associate professor of dermatology, University of Chicago Pritzker School of Medicine, and head, Division of Dermatology, North Shore University Health System, Chicago.


Dr. Kenneth Gordon

"In terms of laboratory values and monitoring of the drug, there does not seem to be a signal that we need to keep close track of patients," said Dr. Gordon, describing the therapy as an anti-inflammatory

Please turn to **Oral biologic** page **14**→

Diagnosis

Cellulitis cases hospitalized more frequently, for longer, in Canada

■ More training, dermatology consults required to prevent misdiagnosis of cases

by EMILY INNES, Assistant Editor, The Chronicle

Misdiagnosis is a probable reason a high percentage of Canadians are hospitalized with cellulitis for prolonged stays and may play a role in the mortality rate of cellulitis patients, according to a database study published in the *Journal of Cutaneous Medicine and Surgery* (Jan. 2014; 18:33-37).

Please turn to **Cellulitis** page **36**→

Clinical practice

New topical for herpes labialis approved for use in Canada

■ Important to initiate new therapy at first sign of prodrome

by EMILY INNES,
Assistant Editor, The Chronicle

The first combination anti-viral and anti-inflammatory agent for treating early signs and symptoms of recurrent herpes labialis was released in Canada in October.

The topical cream, acyclovir 5% and hydrocortisone 1%, which has been on the U.S. market since 2011, was approved by Health Canada for the treatment of cold sores in patients 12 years of age and older.

Dr. Gary Sibbald, a dermatologist and professor of medicine and public health at the University of Toronto, conducted a pivotal study of 230 patients that showed more than two-thirds of participants with this condition preferred using a topical cream over oral therapy, which he said makes the acyclovir 5% and hydrocortisome 1% cream a desirable medication to prescribe.


Dr. Gary Sibbald

Both phases targeted

Dr. Sibbald said the product also targets both phases of the cold sore from the burning and stinging caused by the virus replication as well as the redness, blistering, and ulceration caused by the body's inflammatory response to trying to heal.

"We now have a new and improved vehicle that has shown to be more effective, and one of the ways of measuring the effects of [a cold sore] remedy . . . is to actually look at [the rate of progression to ulceration]," said Dr. Sibbald.

Please turn to **Herpes** page **16**→

HIDDEN BEHIND THE HIGH QUALITY CARE OF EAU THERMALE AVÈNE...
STERILE COSMETICS INVENTED BY PIERRE FABRE LABORATORIES

PIERRE FABRE LABORATORIES INNOVATION Pierre Fabre

AVAILABLE IN DRUGSTORES

TOP of the MONTH

New in acne research: Genotype may increase risk of acne vulgaris
The TIMP-2 (-418 CC) genotype may increase the tendency for patients to develop acne vulgaris by disrupting the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), researchers report **8**

Unexpected behaviour seen in IL-23 signalling pathway in PPP, PPPP
Study regarding efficacy of ustekinumab in the treatment of these conditions reveals unexpected behaviour in the IL-23 signalling pathway. **21**

Chronicle Postgraduate Educational Supplement
In this month's Chronicle Postgraduate Educational Supplement, researchers report on the prevalence, incidence, and predictive factors for hand eczema in young adults in Sweden **29**

CORRECTION

An article in the Dec. 2013 issue of *The Chronicle of Skin & Allergy* ("New Urticaria Guidelines Developed," page 9) incorrectly listed the titles of Dr. Gordon Sussman. Dr. Sussman is Professor of Medicine at the University of Toronto, and a past-president of the Canadian Society of Allergy and Clinical Immunology.

Image courtesy: Onetwo1 at the English language Wikipedia

Research

Acne therapy, from the ocean?

From the News Resources of The Chronicle

Fatty acids sourced from marine algae show some efficacy at inhibiting the growth of P. acnes, potentially representing a novel treatment for acne vulgaris.

The research, published in *Marine Drugs* (2013; 11(11):4544-4557), was undertaken by investigators from the University of Stirling in Scotland. The authors note that the decrease in clinical efficacy of existing topical agents for acne vulgaris has spurred interest in fatty acids for treating the condition, due to their potent, broad-spectrum antimicrobial activity and the lack of resistance to their mechanism of action. The researchers found six fatty acids effective at inhibiting the proliferation of acne bacteria, including eicosapentaenoic acid (EPA) and dihomo-gamma-linolenic acid (DGLA). EPA is produced by marine algae and typically reaches humans through the food chain through consumption of fish, and DGLA is also produced by some types of brown algae.

In the study, the six long-chain polyunsaturated fatty acids (LC-PUFAs) demonstrated this inhibitory ability at concentrations of 32-1024 mg/L against both P. acnes and S. aureus. While the S. aureus were killed after 15 to 30 minutes of exposure, the LC-PUFAs did not appear to be bactericidal against P. acnes. Interestingly, the authors also observed synergistic activity between five of the LC-PUFAs and the aminoglycoside antibiotic NEO, as well as three of the LC-PUFAs and benzoyl peroxide. This suggests the potential for maintaining efficacy at lower doses, which could in turn reduce side effects.

A **Message** from the **Medical Editor**

In this issue of THE CHRONICLE OF SKIN & ALLERGY, we present many articles that will be of great interest to the practicing clinician. One must-read article is New Options for Common Conditions (see page 4). In this article Drs. Landells, Metelitsa, Skotnicki, DeKoven, Donovan and Tan Dytoc update readers on everything from recent advances in pediatric dermatology, contact dermatitis and laser as well as the therapeutic advances in the treatment of HS, chronic spontaneous urticaria and rosacea to name but a few.

After reviewing this article there are two very important points which I believe are worth noting. First and foremost is that Canadian dermatologists continue to play an important role in the clinical trials that lead to these important therapeutic breakthroughs. I know a case of the development of adalimumab for HS. Canadian dermatologists have contributed significantly to that research program. The same can be said for the development of efinaconazole for the treatment of onychomycosis.

The second important aspect of advances in therapeutics include the re-engagement of dermatologists with other specialists. With psoriasis,

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Quoted and noted

"[Antibiotic resistance] is more at the forefront [of our practices] . . . It is not just the oral agents, but I think the biggest change is examining the use of topical [antibiotic] agents."

Dr. Sandy Skotnicki, dermatologist and medical director of the Bay Dermatology Centre in Toronto

(see page 4)

Contacting The Chronicle

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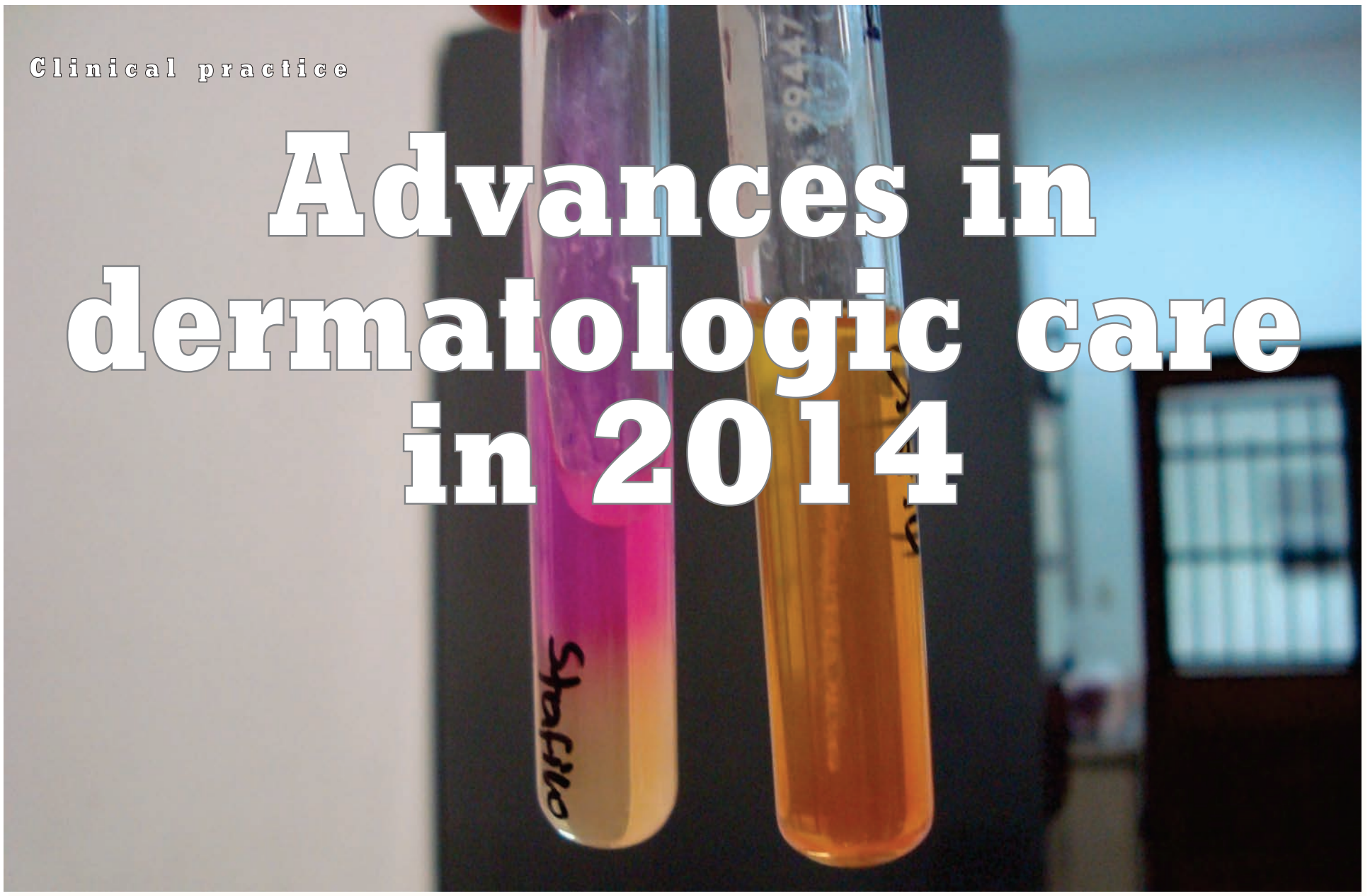


Clinical practice

Advances in dermatologic care in 2014

■ New therapies may provide improved alternatives for patients and clinicians

by LOUISE GAGNON,
Correspondent, The Chronicle

A change in practice in pediatric dermatology to manage hemangiomas, the entry of a new agent to treat nail fungus, and concerns regarding product ingredients that may cause an allergic reaction are three of the newsworthy items in the world of dermatology in 2014.

Propranolol had emerged as an advance in the treatment of infantile hemangiomas a few years ago, but concern about side effects associated with the systemic beta-blocker have seen pediatric dermatologists move to using topical agents with a better safety profile.

Topical beta-blockers

"It was a breakthrough to use oral beta-blockers for the treatment of infantile hemangiomas," explained Dr. Ian Landells, a dermatologist in St. John's, Newfoundland and Labrador

"It has been found that topical beta-blockers can be very effective in suppressing the growth of infantile hemangiomas," said Dr. Landells.

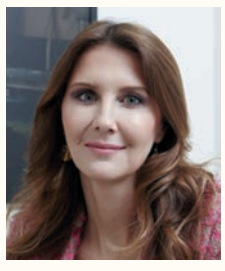
"A beta-blocker like topical timolol 0.5% gel, which is used to treat glaucoma, is clearly much safer than using a systemic agent. It is off-label use, but there are quite a few papers suggesting that it is safe to use. We can put this on and prevent the hemangioma from growing." Dr. Landells is also clinical chief of the Division of Dermatology for Eastern Health, Medical Director (Dermatology) at Nexus Clinical Research, and clinical associate professor in the Faculty of Medicine at Memorial University in St. John's.

Dr. Ian Landells

Dr. Joel DeKoven

Dr. Andrei Metelitsa

Dr. Jeff Donovan



Dr. Sandy Skotnicki

Dr. Marlene Tan Dytoc

Institutions like the Hospital for Sick Children in Toronto have also opted to use an alternative to propranolol, selecting nadolol instead to treat infantile hemangiomas.

Canadian clinicians can now add ustekinumab, a biologic therapy for psoriasis, to their armamentarium of treatments for psoriatic arthritis, pointed out Dr. Landells.

"We used to use this drug for patients who just had psoriasis," said Dr. Landells. "There is now conclusive data out there that it is an effective treatment for psoriatic arthritis as well, and it has consequently been approved by Health Canada for this indication as well as psoriasis. That expands the choice of what we can use for our psoriasis patients who also suffer from psoriatic arthritis."

Emerging agents for onychomycosis, such as efinaconazole 10% topical solution, which received approval in Canada in late 2013, will be an interesting addition to the array

Please turn to New page 18→

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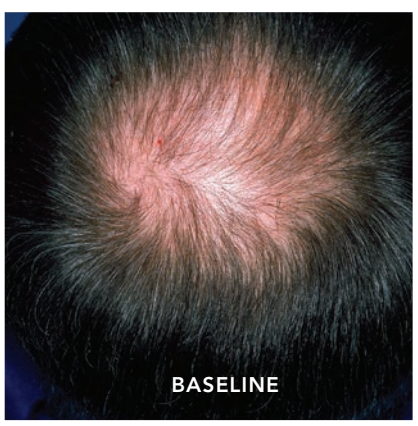

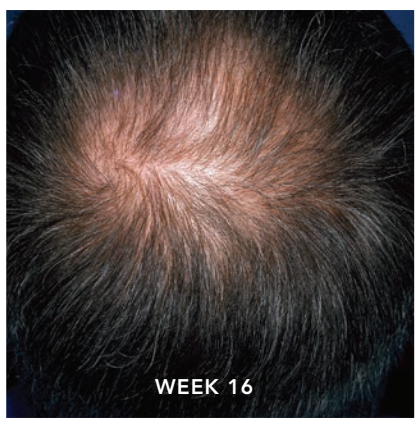

Representative photographs of hair regrowth response for 1 subject at baseline and at week 16. May not be representative of results in all patients.[1]

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- Conditions of clinical use, adverse reactions, drug interactions, and dosing information.

In addition, the page contains the reference list and study parameters relating to this advertisement.

PAAB R&D

See prescribing summary on page 37

Genetic research

ID of candidate genes for KWE ongoing

■ CDF Lecture focuses on etiology, new findings related to keratolytic winter erythema

by LOUISE GAGNON,
Correspondent, The Chronicle

The search continues for candidate genes that are responsible for keratolytic winter erythema (KWE), a rare, autosomal dominant monogenic disorder of epidermal keratinization, according to a professor of medicine and head of the Department of Dermatology at the University of Saskatchewan in Saskatoon.

Delivering the Canadian Dermatology Foundation lecture during the annual meeting of the Canadian Dermatology Association in Quebec City, Dr. Peter Hull noted that KWE, also referred to as Oudtshoorn skin disease, has mainly been identified in South Africa and Germany. No effective treatment exists for the condition, Dr. Hull reported.

"This condition is associated with a cyclical peeling of the palms and soles which gets much worse in the winter months," said Dr. Hull.

Onset usually early in life

Conversely, he added, the condition improves in the summer months. Another characteristic of the condition is increased palmoplantar sweat, which is particularly odourous. An annual migrating erythema is sometimes noted, occurring particularly on the extremities and buttocks but rarely on the trunk, noted Dr. Hull. The condition's onset occurs early in life at about the age of two years, but may be delayed to the teens.

KWE is an entity distinct from epidermolytic palmoplantar keratoderma, a condition that is also characterized by palmoplantar erythema, said Dr. Hull.

The disorder occurs with a prevalence of 1 in every 7,000 South African, Afrikaans-speaking Caucasoid population, a frequency attributed to a founder effect. Genetic research has been conducted to shed light on the condition, explained Dr. Hull.

Want to read the original abstract in the *Journal of Dermatological Science*? Use your smartphone to scan this code, or copy this link into your browser: http://tinyurl.com/lop6ce6

In collaboration with German researchers, KWE was found to be linked to chromosome 8p23.1-22, but mutations in possible candidate genes in the regions were not identified.

Further studies sought to identify disease-associated gene deletions or duplications, but these were not found, Dr. Hull said. Total exon sequencing was also performed, but this proved not to be the magic bullet.

Investigation of candidate genes

Dr. Hull and the collaborative genetic group in South Africa, led by Michele Ramsay, examined gene expression in skin biopsies taken from the soles of patients and controls targeting two promising candidate genes within the region: cathepsin B (CTSB), and farnesyl-diphosphate farnesyltransferase (FDFT1). They used real-time polymerase chain reaction to look at the expression of these two particular candidate genes.

The researchers saw no DNA variants that were isolated exclusively with KWE. While they observed no significant difference in CTSB expression, they did witness a trend to elevated expression of FDFT1 in the skin of affected individuals. After analysis of the FDFT1 promoter region, they attributed this finding to skin inflammation and peeling as they reported in the *Journal of Dermatological Science* (2012 Jan; 65(1):58-62).

Investigators have ruled out CTSB and FDFT1 as candidate genes for KWE, said Dr. Hull. "There is still no Eureka moment."

The identification of candidate genes will likely lead to a greater understanding of the keratinization, cell to cell signalling, and perhaps lead to the development of a therapy for the disorder, he added in conclusion.

Genetic research

Specific genes upregulated in CTCL

■ Genetic markers may help identify patients more likely to have indolent disease

by LOUISE GAGNON, Correspondent, The Chronicle

Investigators have identified some genetic markers that will shed light on which patients who develop cutaneous T-cell lymphoma—a rare cancer but the most common lymphoma cancer of the skin—will have an indolent course of disease.

"We cannot identify based on clinical presentation alone who will progress and who will not," said Dr. Ivan Litvinov, resident in the Division of Dermatology, McGill University Health Centre, Montreal, speaking in Quebec City during the Young Investigators Forum held at the annual meeting of the Canadian Dermatology Association.

About 15 to 20% of patients with stage I disease will progress to higher stages, while approximately 70 to 80% will remain with stable disease, explained Dr. Litvinov. "All stage I patients look the same. If we had a molecular test to identify those patients who will progress, we could spare other patients from toxic treatments and unnecessary tests," said Dr. Litvinov. "There is also an important psychological factor that affects patients and their families who are diagnosed with this cancer, so if we could reassure 70 to 80 per cent of patients, this would have a great positive impact."

Dr. Ivan Litvinov

The disease has been regarded as being very heterogeneous, he noted.

In previous research, Dr. Litvinov and co-investigators conducted microarray and real-time polymerase chain reaction (RT-PCR) analyses of lesional skin from patients with CTCL to detect novel molecular prognostic markers.

They identified three genetic signature patterns for CTCL that correlate with different clinical disease outcomes. They then performed RT-PCR to look at the expression of 160 additional putative tumour suppressor genes and oncogenes in 21 benign inflammatory dermatoses such as psoriasis and eczema, six normal skin samples and 60 CTCL patient skin samples. They looked at six years' worth of clinical data follow-up on all of these patients.

Longer follow-up period analysed

"If the disease does not progress in six years, [the patient] will likely have an indolent disease for the rest of his or her life," said Dr. Litvinov. "Our initial study only had 2.5 years of follow up, so we wanted to look at a longer period of follow-up."

They discovered that two clusters in particular were distinct molecularly, showing a loss of tumour suppressor genes such as BCLA7, DLEU1 and CDKN1C and upregulation of oncogenes such as TOX, JUNB and TCF3, which correlated with poor prognosis.

The other major challenge for clinicians is to be able to reliably diagnose this skin cancer and distinguish it from non-dangerous mimickers such as psoriasis and chronic eczema. When looking at CTCL and benign inflammatory dermatoses, the investigators discovered several genes that were upregulated in CTCL but not in conditions such as eczema, psoriasis, or pityriasis rubra pilaris.

"This demonstrates that inflammatory diseases are different in terms of their molecular make-up," said Dr. Litvinov. "Inflammation in CTCL is different than inflammation in eczema or psoriasis."

The work is far from over, Dr. Litvinov said, and he and his supervisor, Dr. Denis Sasseville, professor of dermatology at McGill University, will continue their research and hope to develop a novel molecular prognostic and diagnostic test for CTCL patients in the coming years.

Their work is supported by the Canadian Dermatology Foundation and Le Fonds de recherche du Québec-Santé (FRQC).

But, what do *you* think?

A question for our readers: Do you have some personal experience relating to the importance of dermatologic research funding by the Canadian Dermatology Foundation or other organization? Let your colleagues know what you think. Send your thoughts to the editors, and we'll report the findings in an upcoming issue.
health@chronicle.org

SPECIAL REPORT

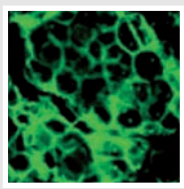
New cleanser maintains skin barrier

May be especially useful for patients with sensitive skin

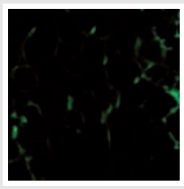
An exclusive formulation of cleanser containing hydrophobically-modified polymers (HMP) is a unique technology that is effective in cleansing the skin, maintaining the skin barrier, and avoiding irritation in patients with sensitive skin.

Speaking in Montreal at Dermatology Update 2013, Menas G. Kizoulis, Scientific Engagement Leader, Johnson & Johnson Consumer Companies, Inc., Skillman, N.J., said many available cleansers can have a detrimental effect on the skin barrier and can cause scaliness, roughness, and dryness.

However, the exclusive HMP technology in Neutrogena Ultra Gentle Daily Cleanser provides patients with effective cleansing and superior lipid barrier preservation. The cleanser helps lower the amount of surfactant that can penetrate the surface of the skin, and delivers the foaming aesthetics and residue-free cleansing many patients prefer.



Skin treated with foaming benchmark cleanser



Skin treated with NEUTROGENA© Ultra Gentle Daily Cleanser

Fluorescence microscopy reveals the degree of surface lipid barrier disruption following treatments with two types of cleansers. More green indicates higher barrier disruption

Cleansers involve several components including water, surfactants, and preservatives, and the nature of the surfactants is vital in ensuring the integrity of the skin barrier, said Kizoulis.

"The purpose of the surfactants is to absorb the dirt and oil on the surface of the skin," he said. "How the surfactants behave in water dictates how effective the cleanser will be and how irritating it will be to your patients."

Increasingly, many products such as moisturizers are being formulated to maintain the skin barrier, but not all cleansers are formulated to maintain the skin barrier, stressed Kizoulis.

Indeed, many surfactants that are contained in over-the-counter cleansers contain a hydrophilic polar head group and a non-polar lipophilic tail, and the surfactants are driven to cleanse the skin. The surfactant in many cleansers is typically at concentrations that are significantly higher than its critical micelle concentration.

"As you cleanse, surfactant monomers, or single units, are coming into contact with the surface of the skin," said Kizoulis. "Not only do they remove the oils, but they absorb and dissolve the lipids such as ceramides and other stratum corneum lipids. They also have an effect on other proteins in the surface of the skin."

ROLE OF STRATUM CORNEUM LIPIDS

Maintaining stratum corneum lipids is essential to maintaining healthy skin, noted Kizoulis.

"All of this disrupts and impairs the barrier," said Kizoulis. "It will also allow for other substances to penetrate through the stratum corneum, causing some inflammatory or oxidative stress response, all leading to redness, dry itching, and uncomfortable sensations."

This effect is not desirable in patients whose skin is not sensitive, but it's particularly bothersome for patients who have conditions like atopic dermatitis, noted Kizoulis. Gentle cleansing is also important for patients with acne and rosacea, and also in patients in whom the skin barrier is defective, added Kizoulis.

Where normal cleansers consist of micelles and single monomers, emerging cleansers contain different properties. Technology has been developed so that cleansers contain a polymer backbone which, when mixed with surfactants in liquid facial cleansers, attach hydrophobically. HMP lead to surfactants assembling into larger structures, which diminish the likelihood of penetration of the skin.

"The micelles bind to the polymer backbone, which has a very positive effect for the skin," said Kizoulis. "You prevent penetration through the barrier and some of the damage normally associated with surfactants."

Studies conducted in vitro looking at the impact of surfactants that contain HMP compared to those that do not contain HMP revealed a decrease in the level of surfactant that penetrates to the stratum corneum when HMP were present.

Research has also shown a difference in the expression of inflammatory markers on the skin when a cleanser made with HMP is used compared to a standard cleanser, said Kizoulis.

AESTHETICALLY PLEASING

In this case, the HMP-based cleanser is designed to have aesthetic appeal (including foaming action, which is preferred by many consumers), and the fragrance is ALLERFREE™ and does not elicit allergic reactions, stressed Kizoulis. (ALLERFREE™ fragrance is considered allergen-free, complying with international standards and with no allergic contact dermatitis reactions observed.) Consumers have expectations that products should be fragrant and aesthetically pleasing, so fragrance is an important consideration—even in individuals with sensitive skin—to ensure they will be compliant with cleansing, he added.

"Consumers expect cleansers to have an aesthetic value, for example, having a fragrance smell left behind on the skin after using the cleanser," said Kizouliz. "The last thing we want is for those individuals to fall back to using standard cleansers because they do not like the [non-fragrant] options available to them."

One three-week double-blind study of 80 subjects with sensitive skin showed Neutrogena Ultra Gentle Daily Cleanser provided improvement in dry, sensitive skin parameters including softness, itching/burning, visible irritation, erythema, and desquamation. The subjects reported a preference for Neutrogena Ultra Gentle Daily Cleanser over a benchmark non-foaming cleanser.

To date, there has been no evidence of the HMP-based cleansers acting as sensitizers for contact dermatitis, noted Kizoulis.

Choosing a good quality skin cleanser can be difficult because while people want to remove unwanted dirt and oils, they need to avoid stripping the protective lipid bilayers on the skin, according to Canadian skin experts. *The Chronicle of Skin & Allergy* spoke with **Dr. Richard Thomas**, a dermatologist at The Face & Skin Clinic in Vancouver, and **Dr. Sandy Skotnicki**, medical director at Bay Dermatology in Toronto, regarding the potential benefits of using a gentle cleanser, such as Johnson & Johnson' Neutrogena facial cleanser with hydrophobically-modified polymers (HMP).

Why can some surfactants in certain cleansers be harmful to the skin—causing irritation, roughness, or dryness?

Dr. Skotnicki: Some of the surfactants have a detergent quality. You want your soap to remove dirt and oil and that is what they are supposed to do, but if they are too strong then they can remove the natural oils that protects your skin and that' when it becomes a problem.

What I mean by detergent is actually what removes oils and so we always use sodium lauryl sulfate as a barometer because [it] is the one that has been around the longest, but it strips the skin of its natural bilayer.

On the outer layer of your skin there is a lipid bilayer, which is what keeps the skin moist and keeps the barrier intact, but when that barrier is destroyed or injured, that is when you get the dry-flakiness of the skin and detergents do that [to the barrier].

How do hydrophobically-modified polymers (HMP) in a cleanser help reduce the negative side-effects associated with some cleansers?

Dr. Thomas: I think this is a clever technology that allows the dirt and the oil in the skin to be broken down… in a gentle way that does not harm, or minimizes the harm, for the skin oil. The fat is broken down and put into little oil bubbles and it does this in a gentle way so these little bubbles don't actually go deeper into the surface and destroy the intrinsic fats.

It seems these bubbles of fat get absorbed into a polymer backbone and it keeps the damage away from the surface. The chemical molecules are big so they absorb these little tiny packets of dirt and oil and they do not sit in small components in the skin, which can penetrate deeper in the skin.

Why is Johnson & Johnson's gentle HMP cleanser particularly good for patients with sensitive skin?

Dr. Thomas: There are people who have skin conditions, such as eczema and rosacea, that make their skin sensitive, and other people have sensitive skin that may be related to the barrier function. A very important component of this barrier function is this fat protein [layer] and if you can cleanse the skin without disrupting the intrinsic barrier components of the skin then it makes it less irritating and therefore better tolerated and will not dry out the skin. That is why this product is nice.

How do patients report feeling after using the J&J gentle cleanser with HMP? Is compliance improved?

Dr. Skotnicki: When you wash yourself [with some] soaps you feel really squeaky clean tight, that is because you just washed away all of the natural moisturizing layers in your skin with the soap. [You are not going to have] that kind of a feeling or sensation with this cleanser, so of course compliance is going to be better.

If you are using acne medication [it can be] very dry and irritating and so if on top of that you are using a soap that is dry and irritating, the combination of the two is going to set you up for failure—your skin is] going to get dry.

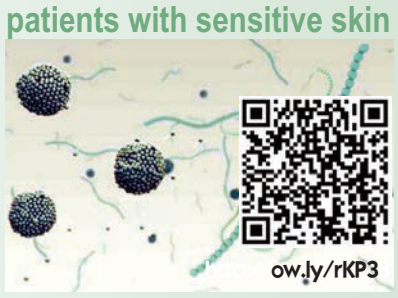
Is this product still effective at removing unwanted dirt and oils from the skin?

Dr. Thomas: The beauty of the chemistry is that it can work effectively as a cleanser, yet keeps the [destruction of] the skin' oil to a minimum and that is the clever part of the technology.

Why is it important for some patients to minimize the use of cleansers with heavy scents? What are the benefits of using an ALLERFREE™ product?

Dr. Thomas: Fragrances can be irritating to the skin and you can actually become allergic to some fragrances. [There is] that challenge, yet, on the other hand in order to have compliance to use the products, they have to leave a very nice aesthetic, nice smelling scent on the skin or else [they won't be used]. There is always a balance to select a fragrance that is low in irritants and low in allergic potential.

WATCH: A cleanser for patients with sensitive skin



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Research

Childhood acne

■ Endocrinology tests usually not needed

From the News Resources of The Chronicle

A focused history and physical examination are sufficient for evaluating the majority of infants and children with acne, with hand X-rays for bone age being a useful screening test, researchers note in an article published online in *Pediatric Dermatology* (Nov. 26, 2013).

Researchers conducted a retrospective chart review of 24 pre-adolescent acne patients, and a related medical literature review. Twelve patients developed acne before 15 months of age, and 12 developed it between two and seven years of age. Most had comedonal lesions, and 75% were female. Some 13 patients had unremarkable laboratory evaluations. Bone age was advanced in one of the 11 children X-rayed. Four patients were diagnosed with premature adrenarche, with additional clinical signs of puberty and growth parameters=>90th percentile, though none required additional treatment. Literature review revealed a third, rare, subset presenting with acne, signs of advanced puberty, and associated endocrinopathy, though this study's authors noted no endocrinopathy among members of their cohort with infantile acne, or in two-thirds of those with childhood-onset acne. The authors note that further evaluation and endocrinology referral are warranted in adolescents with acne showing advanced bone age or additional clinical evidence of early puberty.

Research

More risk with TIMP-2?

■ Genotype may increase acne vulgaris risk

From the News Resources of The Chronicle

The TIMP-2 (-418 CC) genotype may increase the tendency for patients to develop acne vulgaris by disrupting the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), researchers report in *International Journal of Clinical and Experimental Medicine* (Oct. 25, 2013; 6(10):967-972).

Extracellular matrix remodelling, thought to be associated with acne pathogenesis, is regulated by the balance between MMPs and TIMPs, the authors note. They set out to investigate any potential association between MMP-2 (-1306 C/T) and TIMP-2 (-418 G/C) gene polymorphisms and acne risk in a Turkish population. Some 85 subjects presenting at the Dermatology Department of Duzce University Hospital participated. DNA was isolated from 2 mL of each subject's peripheral blood, and their genotypes were analysed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). CC, CT, and TT genotypes for MMP-2 (-1306 C/T) polymorphism were similar between patients and controls (24 [55.8%], 17 [39.5%], and 2 [4.7%], respectively, vs. 21 [50%], 18 [42.9%], and 3 [7.1%], respectively). However, the TIMP-2 (-418 CC) genotype was almost twice as common in the patient group compared to controls (p=0.686, OR=1.45).

Acne update

STUDY REPORTS THAT PHOTOTHERAPY IS EFFECTIVE IN CHINESE PATIENTS WITH ACNE

Phototherapy is effective for moderate to severe acne vulgaris in Chinese patients, according to research published online in *Photodermatology, Photoimmunology, & Photomedicine* (Dec. 9, 2013).

Researchers enrolled 150 patients in a trial—92 male; mean age 28 years—and randomly assigned them to receive photodynamic therapy (PDT), intense pulsed light (IPL), or blue-red light-emitting diode (LED) phototherapy to the right side of the face until their inflammatory lesion count was reduced by =>90%. Patients were examined at one and three months post-treatment. At one month, the researchers determined that =>90% clearance or moderate improvement occured in 46/50 (92%) of PDT patients, 29/50 (58%) of IPL patients, and 22/50 (44%) of LED patients.

The mean number of treatment sessions needed were: PDT 3±1.52; IPL 6±2.15; LED 9±3.34. Mild to moderate pain, erythema, and edema were experienced by 46 (92%) of patients after PDT, which resolved within two hours. After three months, minimal papules and pustules were observed in four PDT patients, seven IPL patients, and 12 LED patients, but there was no recurrence of nodular pustules.

GAG, GGG HAPLOTYPES OF TNF IMPACT ACNE SUSCEPTIBILITY, TIME OF ONSET

Carrying the GAG haplotype of the tumour necrosis factor (TNF) gene is linked with borderline susceptibility to acne vulgaris, while the GGG haplotype appears to be related to earlier onset of the disease in males, researchers report in a paper published online in *Dermatology* (Dec. 10, 2013).

The investigators isolated genomic DNA from 185 patients with acne vulgaris, as well as 165 healthy controls. Single nucleotide polymorphisms at positions -376, -308, and -238 of the promoter region of TNF were then defined. GAG haplotype frequency was greater in those with acne (16.8%) than in controls (9.7%), though significance was borderline (p=0.059).

Males who carried non-GGG haplotypes presented with acne vulgaris at later ages than GGG haplotype carriers. As well, no effect was seen on acne conglobata frequency from the GAG haplotype in women with polycystic ovary syndrome, the researchers reported.

UVB INCREASES INFLAMMATORY CYTOKINE EXPRESSION

Ultraviolet(UV)B exposure significantly increased the expression of inflammatory cytokines in cultured human sebocytes, particularly interleukin(IL)-1ß and IL-8, according to a study published in *The Journal of Dermatology* (Dec. 2013; 40(12):993-997).

The authors note that sebaceous gland hyperplasia and increased sebum secretion after UVB irradiation are widely accepted. To clarify the expression of inflammatory cytokines in cultured sebocytes following UVB irradiation, researchers used polymerase chain reaction to measure gene expression of several inflammatory cytokines in cultured sebocytes after exposure to 40 and 70 mJ/cm^2 of UV-B. These included IL-1ß, IL-6, IL-8, and tumor necrosis factor-a. Protein expression of inflammatory cytokines, as well as lipid production, after UVB exposure were also measured using enzyme-lined immunoassay and lipid analysis kit.

The study authors note that many further studies are expected to be required to gauge the impact of UVB on sebaceous glands and further reveal the pathogenic mechanism of acne.

FRACTIONAL RF, ER-DOPED GLASS FOR ATROPIC SCARS APPEAR TO BE EQUAL

Fractional, bipolar RF and erbium-doped glass 1,550 nm are similarly effective for the treatment of atropic acne scars, according to research published online late last year in *Dermatologic Surgery* (Nov. 25, 2013).

Investigators treated 20 subjects who had atrophic acne scars with three split-face monthly treatments—treating one side with fractional bipolar RF, and one side with fractional erbium-doped glass 1,550 nm. Improvement in acne scars was evaluated at four weeks post-treatment by the patients and three independent physicians, as were any side effects. There were significant improvements in the scars observed after both treatments, without a significant difference between the treatments.

Pain, transient facial erythema, and scab formation occurred with both treatments, and while the fractional erbium-doped glass resulted in a higher pain score than with the RF device, duration of scab shedding was shorter with that treatment.

The researchers reported that one patient experienced postinflammatory hyperpigmentation on the side of their face that was treated with the fractional erbium-doped glass.

Introducing Epuris® (isotretinoin):

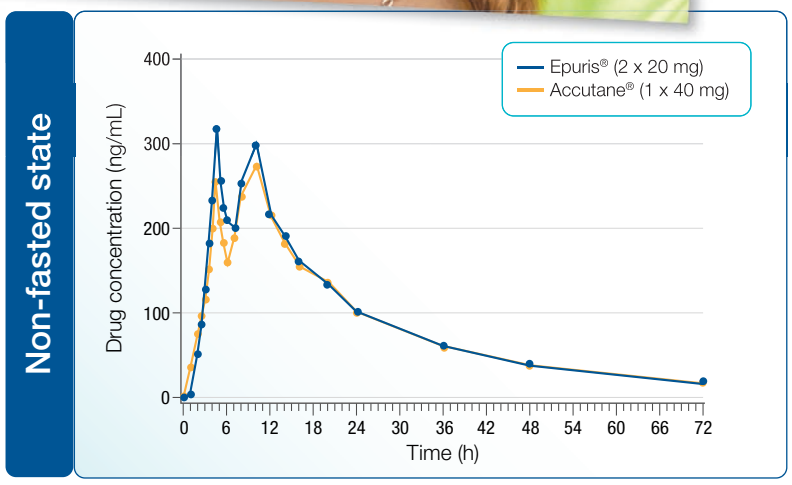
The next generation in severe acne treatment

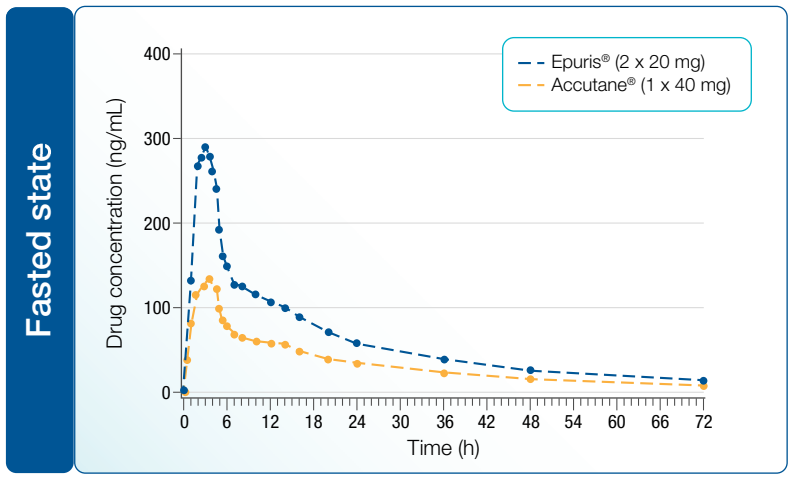
The well-established clinical benefits you know plus the reliable absorption and flexible dosing you need

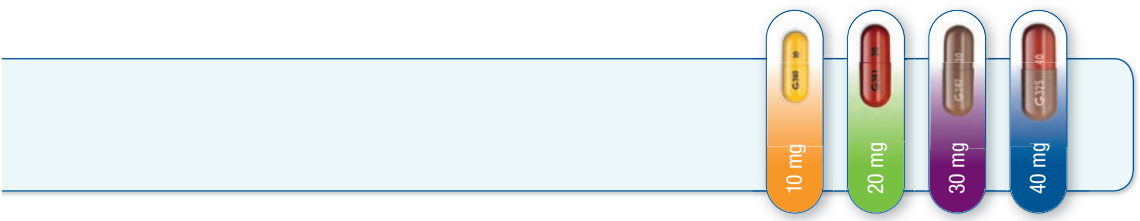
In the fasted state, the absorption of Epuris® was approximately 83% greater than Accutane®.[1]

- When taken with a high-fat meal, Epuris® was equivalent in absorption to Accutane®.[1]
- Pharmacokinetic studies have shown that Epuris® is reliably absorbed in the fasted and non-fasted state.[1]

Plasma concentration of Epuris® vs Accutane® over time in fasted and non-fasted states in healthy volunteers (N = 60)[2]*







- The efficacy and safety profile of Epuris® were consistent with that of other isotretinoin-containing products under fed conditions.[1†]
- Available in four strengths, taken once daily or in two divided doses, for individualized dosing.[1]

Epuris® (isotretinoin) is indicated for the treatment of severe nodular and/or inflammatory acne, acne conglobata and recalcitrant acne in patients aged 12 years or older who are unresponsive to first-line therapies. Epuris® is contraindicated in pregnancy.

Epuris® is NOT INTERCHANGEABLE with other isotretinoin-containing products.

References: **1.** Cipher Pharmaceuticals Inc. Epuris® Product Monograph. March 14, 2013. **2.** Cipher Pharmaceuticals Inc. Data on file, 2013.

*Open-label, single-dose, randomized, crossover pharmacokinetic study of 60 healthy volunteers (aged 18–55 years). Participants randomized to receive Epuris® (2 x 20 mg) or Accutane® (1 x 40 mg) after an overnight fast or high-fat, high-calorie breakfast over four periods with a 21 day washout period in between.

†Double-blind, randomized, Phase 3, parallel-group study of Epuris® vs isotretinoin (reference product) under fed conditions in 925 patients with severe recalcitrant nodular acne randomized to Epuris® or isotretinoin (0.5 mg/kg/day for the first 4 weeks; 1 mg/kg/day for the following 16 weeks). The isotretinoin reference product was a generic formulation.

Refer to the page number on the bottom right for additional safety information and for a web link to the product monograph.

Indications and clinical use: Because of significant side effects associated with its use, Epuris® should be reserved for patients where the conditions listed above are unresponsive to conventional first-line therapies. Epuris® should only be prescribed by physicians knowledgeable in the use of retinoids systemically, who understand the risk of teratogenicity in females of child bearing age and who are experienced in counselling young adults for whom isotretinoin is generally indicated. **Epuris® should not be substituted with other marketed formulations of isotretinoin.** Use of isotretinoin in pediatric patients aged 12–17 years should be given careful consideration, especially those with a known metabolic or structural bone disease. **Contraindications: pregnancy**; breastfeeding women; hepatic and renal insufficiency; hypervitaminosis A; patients with excessively elevated blood lipids; patients taking tetracyclines. **Most serious warnings and precautions: Pregnancy prevention:** Isotretinoin is a known teratogen contraindicated in pregnancy. Epuris® is also contraindicated in females of childbearing potential and should only be prescribed if **ALL** the conditions described in the Product Monograph under "Conditions of use" are met. Physicians **MUST** use the Epuris® Patient Engagement and Education Resource (PEER™) Program when prescribing this drug to female patients of childbearing potential. **Psychiatric:** Some patients treated with isotretinoin have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression during therapy. **Neurologic:** Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. **Other relevant warnings and precautions:** The most common reported side effects are mucocutaneous or dermatologic. However, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

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See prescribing summary on page 36

Advances in AK Treatment

Picato® One year in clinical use

Ingenol mebuate gel (Picato®, LEO Pharma), a novel therapy derived from the sap of the Euphorbia peplus plant and indicated for the topical treatment of actinic keratosis, has now been available for clinical use in Canada approaching one year. During that time, clinicians across the country have gained experience with the unique therapy and many have learned more during major dermatology conferences—including the annual meetings of the Canadian Dermatology Association and the European Academy of Dermatology and Venereology, and the Las Vegas Fall Clinical Dermatology Meeting—where Picato® was the topic of several presentations.

The first and only topical AK therapy that can be used for as short as two or three days, Picato® is designed for two different treatment approaches—a 0.015% concentration for treating a field of up to 25 cm² on the face and scalp over three days, and a 0.05% concentration for a two-day treatment on the trunk and extremities.

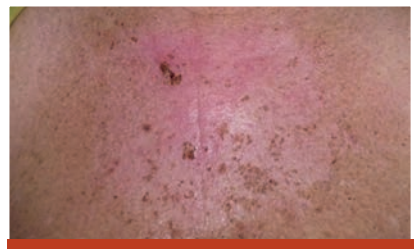
To obtain a perspective on the use of Picato® in clinical practice, *The Chronicle of Skin & Allergy* spoke with three leading dermatologists regarding their experiences with this novel therapy: Dr. Gary Goldenberg, Medical Director of the Dermatology Faculty Practice at The Mount Sinai Medical Centre in New York City, Dr. Melinda Gooderham, dermatologist and Medical Director at the SKiN Centre for Dermatology in Peterborough, Ont. and Dr. George M. Martin, a dermatologist at the Dermatology and Laser Center of Maui in Hawaii.

What is unique about Picato® therapy?

Dr. Martin: Picato® fits into a group of therapies that have limited downtime, and excellent compliance. In today's world people can't have a lot of downtime where they are looking socially unacceptable. That includes retirees, who are very busy with their social lives. They don't want to spend weeks and months with crusting and weeping and looking socially unacceptable, particularly when their face is treated for actinic keratosis. As you look at the original study designs of most of the other [AK] drugs, the therapeutic downtime was in some cases as long as 16 weeks, and in most cases several weeks to months.

The beauty of Picato® is that you have, at least for the face, three applications. Then that's followed by a week of crusting and healing. So basically, if they are treated on a weekend, a Friday, Saturday and Sunday, the following Monday, seven days after termination of therapy, they can return to work.

Dr. Goldenberg: Compliance with this therapy is very high. Nothing is 100 per cent, but it is close to 100 per cent. I think that the entire duration of time that the patient is red is shortened because therapy is short. For most AK patients, the duration of erythema is about the duration of the treatment plus two weeks, because that's how long it usually takes for the skin to normally turn over.



Ingenol Mebutate .015% Gel: Day 12 post-treatment

Dr. Gooderham: The treatment itself for the face and scalp is only three days, with an inflammatory reaction lasting about one week. But then it is completely cleared up by day 15, where the other therapies are just ramping up by then—5-fluorouracil takes three weeks, with a healing time after that. For [imiquimod 3.75%], the total treatment time is six weeks, and [imiquimod 5%] can be anywhere from eight to sixteen weeks. So with Picato®, the patients are back to normal within two weeks, and none of the other topical, patient-applied treatments are that quick. With cryotherapy you have about a week or two of healing, but it is a lesion-directed therapy. With Picato®, you're treating the whole field.

When should Picato® be your first choice for therapy?

Dr. Goldenberg: It depends on how big the area is where they have AKs. Let's say it is a smaller-sized person and their entire face is affected. You can actually stretch out one of those little tubes [of Picato®] to cover the entire face. If the patient is a large person, then it is harder to cover their entire face. But I think it is a great choice in any patient with actinic keratosis, especially ones who cannot tolerate being red for a long period of time.

Dr. Gooderham: [I would say] if they have field cancerization. So it is not the single AK, it is more in a wide area like an entire forehead where they have lesions, or on their cheeks or temples. If the patient had one AK on their forehead and one on their ear and one on their hand, they would not be the best patient for field therapy. You want them when [the AKs are] concentrated in an area. We call that field cancerization.

Dr. Martin: As far as the 0.05 for the trunk and extremities, the data is very strong but it is skewed toward really good efficacy on the chest. The efficacy starts to fall off when we start to talk about the extremities, as it does for most therapies. Treating extremities is very difficult for all field therapies. They all have less than adequate data, and in some cases we have to treat with two modalities in combination. For example, using 5-fluorouracil and imiquimod in combination, just to get significant efficacy. So Picato® 0.05 for the chest is great.

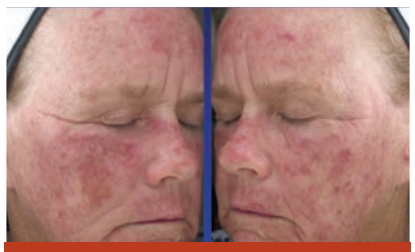
What can you tell readers regarding Picato®'s mechanism of action?

Dr. Goldenberg: Picato® works using two mechanisms. One, it gets absorbed into the cells and inhibits mitochondria in those cells from producing energy. When the cells don't produce energy, they die off. [Picato®] actually balloons the mitochondria so the cell bursts. Then, it induces an immune response in the

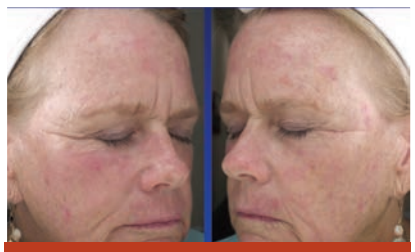
Dr. Goldenberg

Dr. Gooderham

Dr. Martin



Day 4 - Ingenol Mebutate .015% x 3 days 1 day AFTER completing Tx



Day 12 - Ingenol Mebutate .015% x 3 days 8 days AFTER completing Tx

area where the abnormal cells are.

Dr. Martin: The mechanism of action of Picato®is really two-fold. Initially there is a direct cytotoxic effect—more to atypical cells, but to the skin. If you look at the science behind it, it is driven by PKC—a protein kinase C reaction. It creates a reaction almost like a chemical peel with swelling, redness and discomfort. That usually happens four hours after application.

That is followed by a more specific reaction in which rapidly dividing keratinocytes such as those you see in actinic keratosis and endothelial cells, will be stimulated to produce the cytokine IL-8, a chemo-attractant. It recruits neutrophils. So there is this intense neutrophil infiltration, and that's responsible for more of the selective destruction of AKs compared to normal skin.

Dr. Gooderham: There is a combination where you get a cell-mediated reaction—you get some immune cells coming—but you also get a kind of destructive mechanism. [There is] an immediate destructive action upon application of the medication, when it is at a higher concentration. Then as the medication bears down and is at a lower concentration, [there is] a stimulation of cellular response.

Can Picato® be used in conjunction with other actinic keratosis therapies?

Dr. Goldenberg: There was a study we just finished called FIELD Study 1 [http://tinyurl.com/l3t7yda]. The data that is in the public domain that I can tell you about, is that at 11 weeks, patients who underwent Picato®and cryosurgery, did better than those who underwent cryosurgery alone.

Dr. Martin: [Other researchers] are looking more into sequential therapy. Because of Picato®'s unique mechanism of action with the initial cytotoxicity and the skin reactivity, it makes combining with topical therapy difficult. Overlapping, like same-day or alternating-day therapy, is difficult. I think that if it is going to be used in conjunction with another therapy, it might best be used sequentially.

Dr. Gooderham: There was one group in the U.S. that combined cryotherapy and Picato®. So that was one randomized, controlled trial. That was done by Mark Lebwohl's group. As far as I know, there have been no other studies done on it, but I know just from anecdotal evidence, that some people are combining therapy. They might do one course of 5-fluorouracil and clear up some lesions, but if they're not all cleared maybe follow it with Picato®, where you are basically doing cycling between the treatments.

Overall, what has your experience been with Picato®?

Dr. Goldenberg: I've actually had a very positive experience working with the drug. I think it is a very interesting molecule. I think patients do extremely well with it. I think the fact that it is a very short duration of therapy reassures me that they're going to be compliant with it. That's really the name of the game, because if you can get somebody to do something, it is much easier to get them to do it for a few days than for an extended period of time. And I think the efficacy from the drug is very good.

Dr. Martin: I think we've had great success expanding the field of therapy from 25 square cm to full face, full scalp, full chest, the hands, and somewhat up the forearms. The trunk and chest are very responsive to the 0.05 concentration, and it is very dramatic and patients are really satisfied. We get great compliance so long as patients are counselled in advance, and expectations are set.

On the hands, forearms and extremities, we're trying to improve the efficacy of Picato®by allowing more of the drug to get in and do its job. It turns out that in the hands, forearms and extremities, the combination of the thickness of the actinic keratosis and the thickness of the skin, make every one of [the topical agents for actinic keratosis] less effective and safe. That's the reason for the use of combination therapy in those areas.

Dr. Gooderham: It's great. There a few things you have to warn patients about: The inflammatory reaction, and how, because neutrophils are the main cells that are attracted to the site, it looks very pustular. So you reassure [patients] that it is not an infection, warning them that if they are using it on the face, they can get eyelid edema. You need to prepare the patients, but it actually works really well.

EADV poster sessions reveal new information about ingenol mebutate

By **Dr. Charles Lynde**, reporting from the annual meeting of the European Academy of Dermatology and Venereology, Istanbul, Oct. 2013.

Ingenol mebutate is a new topical therapy indicated for the treatment of actinic keratosis of the face, hands, neck and extremities. Several posters at the annual conference of the European Academy of Dermatology and Venereology, held in Istanbul in Oct. 2013, dealt with the benefits of this new molecule.

A consensus approach to topical treatment for actinic keratosis

A modified Delphi expert session involving seven dermatologists specializing in actinic keratosis from the U.S., Brazil, Germany, the U.K., Italy, France and Spain was convened. These experts reviewed and discussed findings from prior research into physicians' perceptions of actinic keratosis and topical treatments.

Facilitated discussion generated consensus on a number of items. It was felt treatment of actinic keratosis would benefit from topical therapies which have a shorter duration and/or a simpler treatment regimen than present existing topical therapies. This would encourage adherence and persistence and thus produce real world efficacy and better outcomes.

It was also felt there was a need for greater awareness of actinic keratoses and its progression to squamous cell carcinoma with clearer information including statistics on the disease, different treatments, efficacy, local skin reactions, and precancerous risks should be available. Several modes of communication to patients and physicians should be available.

Effect of ingenol mebutate gel on treatment satisfaction and quality of life in actinic keratosis

Ingenol mebutate gel is indicated for the topical treatment of actinic keratosis in adults. This therapy can entail local skin reactions that are potentially unsightly and associated with pain, discomfort, and disruption of daily activities.

Patients received therapy with either vehicle or ingenol mebutate gel for self-application on the face and scalp or trunk and extremities, and were followed up for 57 days in a phase 3 multicentre, randomized, double blind, vehicle-controlled trial. Treatment Satisfaction Questionnaire for Medication (TSQM) was self-assessed on day 57. In addition, the Skindex-16 survey was self-administered on days 1, 8, 29, and 57. Post-hoc exploratory regression analyses were performed to investigate association between the effective treatment on the TSQM/Skindex-16 and the degree of lesion clearance.

A total of 1,005 patients were randomized: 547 in the face and scalp group and 458 in the extremities group. The results of this trial suggest patients with either complete or partial clearance experienced a meaningful quality of life improvement with ingenol mebutate.

Ingenol mebutate gel 0.05% is efficacious in treating subclinical actinic keratosis in a field of cancerization

Reflectance confocal microscopy allows non-invasive imaging and monitoring of skin lesions at near histological resolution. Sixteen patients were randomized to either ingenol mebutate 0.05% or vehicle gel for actinic field cancerization. Based on clinical assessment, the local complete clearance of actinic keratoses in the field was 14 out of 32 actinic keratotic lesions with ingenol mebutate, and one out of 16 with vehicle gel.

Based on the RCM visualized honeycomb grading, ingenol mebutate completely cleared 11 out of 32 visualized actinic keratotic lesions and 23 of the 32 sub-clinical actinic keratotic lesions on day 57.

Ingenol mebutate gel represents a novel effective treatment for actinic field cancerization. This is the first study that has assessed the ability of ingenol mebutate gel to clear subclinical lesions in the treatment field.

Evaluation of topical treatment with ingenol mebutate gel 0.015%, three weeks after cryosurgery of actinic keratosis on the face and scalp

Although cryosurgery effectively treats individual targeted lesions of actinic keratoses, recurrence rates are high and the procedure fails to address field cancerization of perilesional skin.

In this 11-week analysis of a phase 3 randomized double blind vehicle controlled 12-month study, patients received liquid nitrogen cryotherapy to all visible actinic keratoses, and, after a three-week healing period, then received once daily treatment with either ingenol mebutate gel 0.015% or vehicle gel for three consecutive days. A total of 329 randomized patients were treated with ingenol mebutate gel (n = 167) or vehicle gel (n = 162) after cryotherapy. The percentage of patients who achieved complete clearance were significantly higher in the ingenol mebutate group than in the vehicle group, 60.5% versus 49.4%. This study analysis shows that the short term rate of complete clearance of actinic keratoses on the face and scalp was improved after sequential topical treatment with ingenol mebutate gel 0.015% following cryotherapy. This is significant in that this is often how topical field cancerization therapies are used in combination with cryotherapy, and confirms real life methods of use.

Dr. Lynde is Associate Professor of Medicine at the University of Toronto's Department of Medicine, and Director of the Lynde Centre for Dermatology, Markham, Ont.

Supplement to *The Chronicle of Skin & Allergy,* February 2014. Chronicle is an independent medical news service that provides educational updates regarding medical developments around the world. Views expressed are those of the participants and do not necessarily reflect those of the publisher or sponsor.

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Research

AD and TSLP

■ Variant associated with less persistence

From the News Resources of The Chronicle

A variation in thymic stromal lymphopoietin (TSLP) is associated with less persistent atopic dermatitis (AD) in children, potentially representing a therapeutic target for the treatment of AD, particularly where barrier function is diminished due to filaggrin protein (FLG) mutations, researchers report online in *JAMA Dermatology* (Jan. 8, 2014).

A prospective cohort study was carried out, involving 796 children who were enrolled in the U.S. Pediatric Eczema Elective Registry. TSLP variation was evaluated, and the main outcome measure was self-reported clearance of AD symptoms and no requirement of medication for six months, recorded at six-month intervals.

The authors evaluated 14 TSLP variants. Variant rs1898671 was significantly associated with the outcome in Caucasian children ($p=0.01$). Measuring by overlapping confidence intervals (CI), similar odds ratios (ORs) were seen among white children (OR 1.72; 95% CI, 1.11-2.66) and African Americans (OR 1.33; 95% CI, 0.52-3.45). In individuals with an FLG loss-of-function mutation, those children who also had a TSLP variation were found to be more likely to have less-persistent disease (OR 4.92; 95% CI, 2.04-11.86).

Research

Videodermoscopy

■ Helpful in Dx of clinically doubtful lesions

From the News Resources of The Chronicle

Videodermoscopy should be considered an important additional tool in the diagnosis of clinically doubtful erythematous desquamative lesions in children, because it allows the confirmation or exclusion of a psoriatic vascular pattern. Videodermoscopy also demonstrates some advantages over skin biopsy, investigators report online in *Pediatric Dermatology* (Jan. 3, 2014).

Some 60 Caucasian children were enrolled into the open comparative study, and divided into two groups. The 24 patients in Group A had multiple plaque psoriasis, and the 36 patients in Group B had other erythematous desquamative disorders. At least two of each patient's lesions were examined using videodermatoscopy at 150x magnification, with the supervicial vascular pattern of each lesion evaluated in three different fields.

In the lesions from Group A, all considered plaques showed dilated capillaries with a "bushy" aspect which were homogeneously distributed in all the examined fields. However in Group B, the videodermatoscopic findings were not specific—with some showing normal-looking capillaries, slightly dilated vessels, or only a few isolated "bushes."

Pediatric dermatology update

VARIATION IN CLINICAL EXPRESSION OF HFMD IN CHILDREN

The clinical expression of hand, foot, and mouth disease (HFMD) in children presents in a spectrum from classical to generalized vesicular exanthema, with generalized and atypical exanthema observed in the CV-A6 and CV-A16 variants, and CV-A6 also being associated with peri-oral rash, according to a study published online in *The Pediatric Infectious Disease Journal* (Jan. 23, 2014).

Researchers carried out a prospective, cross-sectional study in seven pediatric dermatology units in France. All children with a clinically suspected diagnosis of HFMD from Mar. 2010 to Feb. 2012 were included. Clinical data was collected, and nasopharynx and vesicle swabs were taken for real-time PCR (RT-PCR) and genotyping. Those children with a clinical diagnosis of HFMD and positive enterovirus PCR results were included in the final analysis.

Of the 104 children with suspected HFMD, 89 had confirmed HFMD (mean age 25.7 months, M/F sex ratio 1.54). Among the confirmed HFMD cases, 78 (87.5%) had lesions outside of the typical hands, feet, and mouth areas, 37 (41.5%) had involvement in five or more anatomical regions (HFM, buttocks, legs, arms, and trunk), which was considered widespread exanthema. Widespread vesicular exanthema was observed with both CV-A6 and CV-A16 variants of the infection, and peri-oral rash was associated with CV-A6 ($p<0.001$).

EPIDERMOLYSIS BULLOSA CARE INCONSISTENT ACROSS U.S., CANADA

Uniformity of care for epidermolysis bullosa (EB) is lacking in the U.S. and Canada, and the development and acceptance of evidence-based guidelines and outcome measures for EB care may improve this situation, according to the results of a survey published online in *Pediatric Dermatology* (Jan. 23, 2014).

The authors conducted an online survey of attending physicians experienced with care of EB, with participants sourced from Canadian and U.S. resident members of the Society for Pediatric Dermatology. Assessed parameters included number of clinic visits, the availablity of subspecialists, and performance of surveillance studies. Some 56 completed surveys were analysed, with most providers seeing between one and 10 individuals with EB per year in a general dermatology clinic.

Considerable variability was seen between EB types in frequency of clinic visits, the availablity and use of specialists, and the use of laboratory and imaging studies. There was some observed agreement in the frequency of follow-up for infants with more severe EB types, as well as for the components of a history, physical, and routine laboratory studies.

THYROID FUNCTION SHOULD BE TESTED IN CHILDHOOD VITILIGO

In children with vitiligo, thyroid function tests and thyroid autoantibodies should be analysed, researchers suggest based on the findings from a study published in the *Indian Journal of Endocrinology and Metabolism* (Nov. 2013; 17(6):1096-1099).

The authors retrospectively studied the laboratory documents of 79 pediatric vitiligo patients who applied to a single pediatric dermatology clinic between Apr. 2008 and Jan. 2010. Data on thyroid function tests (FT3, FT4, and TSH), and thyroid autoantibodies (TgAb and TPOAb) were examined. Abnormalities in the tests and autoantibodies were detected in 25.3% (20) of participants. Of those, 13 (16.4%) were evaluated as having subclinical hypothyroidism, two (2.5%) were evaluated as hypothyroidism, and five (6.3%) were evaluated as euthyroidism. As well, nine (11.3%) patients were positive for thyroid autoantibodies. Among the children with vitiligo, previously reported thyroid disease prevalence varied from 10.7% to 24.1%, and the 25.3% prevalence this study found was compatible with the literature.

The high rate of preclinical hypothyroidism pointed to a likelihood of the development of overt hypothyroidism in the longer term.

CHARACTERISTICS OF GENITAL NEVI CLARIFIED IN REVIEW

Increased awareness among clinicians of the clinical characteristics, dermatoscopic features, and evolution of genital melanocytic nevi in children may help avoid unnecessary surgery, according to research published online in *Journal of the American Academy of Dermatology* (Dec. 24, 2013).

Noting that the prevalence and characteristics of genital melanocytic nevi in children are not well known, the authors sought to clarify this by performing a chart review. Charts of 1159 children diagnosed with melanocytic nevi over 11 years were examined, and those with genital nevus as a chief symptom were contacted for a follow-up.

Genital nevus prevalence among the children and adolescents evaluated for nevi was 3.5%, or 40 of the 1,159 total evaluated. Of those, the male:female ratio was 1.3:1. No statistically significant differences were seen between patients with and without genital nevi regarding age, sex, total number of nevi, presence of acral and scalp nevi, or family history of dysplastic nevi and melanoma. In 63.6% of patients, the onset of genital nevus was prior to age two. As well, a globular dermatoscopic pattern was seen in 93.3% of patients. Most of the genital nevi gradually changed in diameter, elevation—becoming soft papules—colour, texture, or a combination of these factors. No melanoma or other adverse outcomes were observed after a mean follow-up of 1.5 years.

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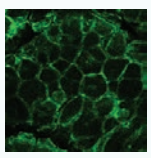
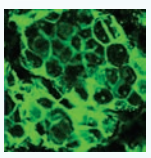
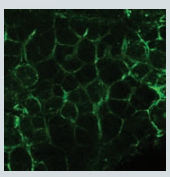


Skin treated with water only



Skin treated with foaming benchmark cleanser



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Oral biologic *next advance for treatment of psoriasis*

Continued from page 1

medicine that has already demonstrated safety in the treatment of psoriatic arthritis.

The availability of the therapy in an oral form makes it potentially attractive to patients who have steered clear of biologic medicines that are typically injected or infused, making the therapy a possible avenue to capture patients with psoriasis who have gone without effective treatment, said Dr. Gordon.

Patients may prefer pills to injections

"The perception is that [pills] are safer than biologic [injections]," he said. "Many patients are concerned about taking shots. For whatever reason, their sense is that pills are better."

The key outcome from the ESTEEM 1 was that about one-third of patients achieved a 75% or more decrease in the Psoriasis Area Severity Index (PASI-75) score in a 16-week period, significantly more than those on placebo. More than half (58.7%) achieved the PASI-50, again significantly more than those on placebo.

Dr. Gordon described patients who were recruited to the trial as a study population that is "very typical", with most having body surface area involvement of more than 10%. Most patients recruited to the trial had body mass indices exceeding 30 kg/m^2. Dr. Gordon noted no pediatric data on apremilast are yet available.

The therapy was also effective in managing nail psoriasis and scalp psoriasis, according to Dr. Gordon.

Specifically, patients treated with apremilast had greater improvements in the Nail Psoriasis Severity Index scores than those treated with placebo, with an improvement of 22.5% vs. a decline of 6.5%, a difference that was statistically significant at p<0.0001.

After 16 weeks of therapy, significantly more patients treated with apremilast achieved a Scalp Physician's Global Assessment score signifying clear or almost clear compared with those treated with placebo, 46.5% vs. 17.5%, p<0.0001.

There is a distinction between safety and tolerability, stressed Dr. Gordon, noting there were slightly more adverse events among patients who were treated with apremilast compared to those on placebo.

"Tolerability are nuisance things but are not [related to] safety," said Dr. Gordon.

"Diarrhea, nausea, and headache seem to be more pronounced in the apremilast group. They represent significant tolerability issues, but most patients will get better after a couple of weeks."

Nausea and vomiting were most frequent in the first week of active treatment in the trial, and those adverse events declined subsequently.

> *"The perception is that pills are safer than biologic [injections]. Many patients are concerned about taking shots. For whatever reason, their sense is that pills are better."*
>
> *—Dr. Kenneth Gordon*

The drop-out rates were comparable between the treatment and placebo arms, with a 10% drop-out rate in the treatment arm and 12% in the placebo arm.

One of the challenges in recruiting patients for psoriasis trials is that it is proving difficult to find patients with psoriasis who have not been exposed to systemic therapies, noted Dr. Gordon.

"It is taking longer to enrol patients in trials because so many patients have been exposed to systemic therapies over time," said Dr. Gordon.

More data from ESTEEM 1 and ESTEEM 2 will be presented at the annual meeting of the American Academy of Dermatology in Denver in Mar. 2014, noted Dr. Gordon.

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Reference: 1. CLINDOXYL® ADV Gel Product Monograph. GlaxoSmithKline Inc., April 2, 2012.

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Herpes labialis *therapy effective from first symptom*

Continued from page 1

During a pilot study with 2,437 participants with a history of herpes simplex labialis, 42% of patients who used the acyclovir 5% and hydrocortisone 1% did not develop an ulcerative lesion compared to 35% of patients who used acyclovir 5% cream and 26% of patients taking a placebo (*J Am Acad Dermatol* April, 2011; 64(4):696.e1-696.e11).

"In essence we have something that works at the first sign," said Dr. Sibbald. "It can work almost immediately. It is important to start the cream at the first sign of burning and stinging and that is in the prodromes or the early redness stage, or when you see something on the skin . . . I don't think it can often completely abort the episode, but it can certainly make the episode more minor and not lead to the ulcer stage."

It is important for patients who have recurrent episodes to have the medication readily available to be applied at the first sign of a cold sore, said Dr. Sibbald.

Patients should watch triggers

He said patients are often aware of their cold sore triggers such as stress, being overtired, co-existing infections, and ultraviolet light exposure.

One tube of the cream should last for one cold sore episode; the product needs to be applied five times a day for five days.

Contraindications include patients with a known or suspected history of hypersensitivity to valacyclovir. The label warns the product should be avoided by pregnant women, nursing women and immunocompromised patients. The label also cautions the therapy may increase the risk of skin infections.

Dr. Sibbald said he is pleased to see an advancement in cold sore treatments because recurring herpes labialis can cause a great burden for some patients, especially in the early stages when they need to avoid direct contact with other people to prevent the spread of the virus.

"[Cold sores] really do, for a lot of patients, have a negative social stigma and a negative social effect—avoiding intimate contact with others, there is a sense of embarrassment, there is a sense of low self-esteem, and for some people it really curbs activities of daily living," said Dr. Sibbald.

He said it is important for physicians to take cold sores seriously, because for some patients they can be painful, can recur often, and can last upwards of two to three weeks.

Cold sores not trivial

"I think it is important that we don't take cold sores as being trivial because to a patient they can be very meaningful," he said.

To practice patient preference-centered care, according to Dr. Sibbald, physicians should recognize that four oral pills taken once at onset and again six to eight hours later can seem like a lot of oral medication, and the patient might prefer to use a topical cream.

"A patient is more likely to adhere to treatment if you give them a treatment they are comfortable with and they understand how the treatment is working," said Dr. Sibbald.

The health care professionals often select oral treatments, because there has not been anything else more effective until recently, he said.

He said the acyclovir 5% and hydrocortisone 1% cream is a popular cream in the U.S., and he expects it will soon become more commonly prescribed in Canada.

Non-proprietary and brand name of therapy: *acyclovir 5% and hydrocortisone 1% (Xerese, Valeant).*

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Help them face their acne

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New therapies *help address issue of antibiotic resistance*

Continued from page 4

of medications to treat the condition, according to Dr. Landells.

"The efficacy is close to what we see with systemic agents," explained Dr. Landells. "We sometimes hesitate to use systemic agents in elderly patients or patients on other medications. I see a lot of patients with nail fungus, and I don't necessarily want to put them on a systemic agent or they don't want to be on a systemic agent."

Dr. Andrei Metelitsa, medical co-director of the Institute for Skin Advancement in Calgary and clinical assistant professor at the University of Calgary in Calgary, also expresses enthusiasm about the new topical to treat toenail fungus.

Topical agent for onychomycosis

"Onychomyosis remains a challenge to treat," said Dr. Metelitsa. "We have topical agents that have limited efficacy, and we have well-known systemic agents, but clinicians are hesitant to use them [the systemic agents] especially when they hear about rare side effects like hepatotoxicity. Lasers can be quite efficacious, but some patients find them very expensive. The future arrival of a new topical agent, efinaconazole 10% solution, represents an exciting new treatment for this condition."

Patients with cold sores can now choose a topical agent that features hydrocortisone added to acyclovir, for herpes simplex labialis. The modified formulation has not resulted in the emergence of viral resistance to acyclovir.

"Hydrocortisone is new, and it decreases the healing time," said Dr. Sandy Skotnicki, assistant professor in the Divisions of Dermatology and Environmental and Occupational Health at the University of Toronto, and staff consultant at St. Michael's Hospital. "It makes sense because an anti-inflammatory has been added [to acyclovir]. Patients are asking for it."

Reducing antibiotic resistance

The challenge to reduce the potential for the development of antibiotic resistance is definitely on the radar for practicing dermatologists. They welcomed therapies in 2013 such as doxycycline monohydrate 40 mg capsules, indicated for the treatment of rosacea and formulated so that the doses are sub-antimicrobial. They are also cognizant that other practices, apart from the prescription of systemic agents, can contribute to the problem of antibiotic resistance.

"[Antibiotic resistance] is more at the forefront [of our practices]," said Dr. Skotnicki. "It is not just the oral agents, but I think the biggest change is examining the use of topical [antibiotic] agents. When people get a sore or cut, they are automatically putting on [polymixin B and bacitracin zinc]. They should not use an antibiotic unless there is an infection [present]. They are treating normal skin flora with an antibiotic. There is a paradigm shift. We tell our patients to avoid using [polymixin B and bacitracin zinc] on cuts."

A study published in 2011 suggested topical antibiotic ointments may contribute to the development of antibiotic resistance (*J Am Acad Derm* 2011 Mar; 64(3 Suppl):S23-29).

Dr. Joel DeKoven, associate professor in the Division of Dermatology at the University of Toronto in Toronto, a consultant dermatologist at Sunnybrook Hospital and St. Michael's Hospital in Toronto, and a member of the North American Contact Dermatitis Group, said that methylisothiazolinone (MI), a compound deservedly named Allergen of the Year in 2013 and found in thousands of cosmetic and industrial products, continues to be an important source of contact allergy.

"It appears the percentage of people who present with MI contact allergy continues to increase, and there have been a number of editorials in *Dermatitis* and *Contact Dermatitis* about the topic," said Dr. DeKoven. "There's a lot of lobbying on the part of dermatologists in Europe and North America to get MI out of products."

Other contact allergens noted

Benzophenones, commonly found in sunscreens, have been named the Allergen of the Year for 2014, but Dr. DeKoven noted a very small percentage of patients, less than 1%, who undergo patch testing react to benzophenones so it would certainly "not be considered for the Allergen of the Year Hall of Fame."

"Benzophenones have been incorporated in sunscreens for several decades," said Dr. DeKoven. "And more and more sunscreen is being used. Yet in practice, we are not seeing significant numbers of people reacting to them. As dermatologists, one of our primary public health messages is Sun Safety. If patients happen to react to benzophenones, there are a number of sunscreens available that we can recommment that do not contain these agents, said Dr. DeKoven.

Prosthetic implant materials such as nickel and cobalt, used in the manufacturing of permanent prosthetic devices for the purposes of knee replacement and hip replacement, continue to represent a possible

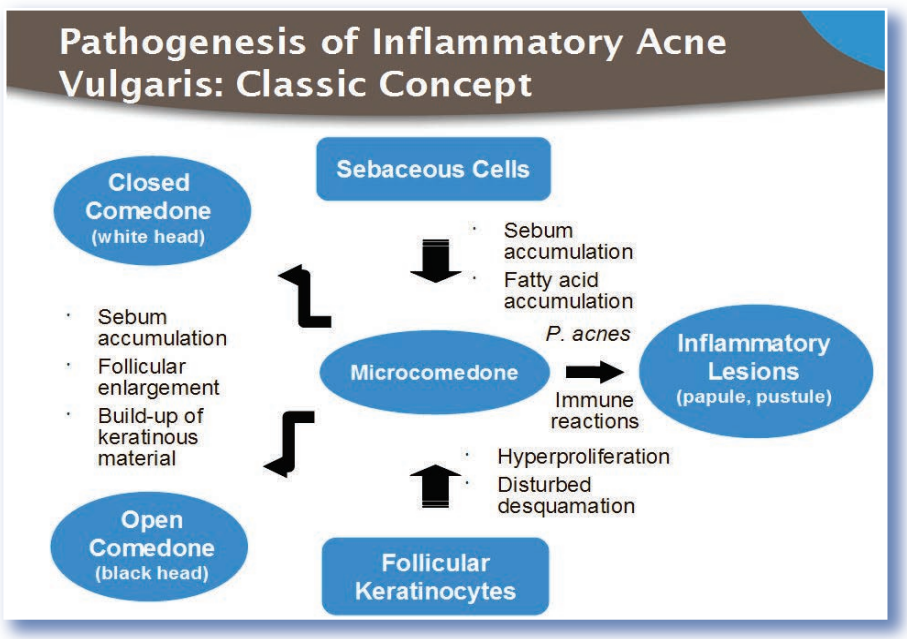
Please turn to **Advances** page **27**→

New understandings of the role of inflammation in the pathogenesis of acne

The traditional model of inflammatory acne pathogenesis and progression is under review by researchers and clinicians and may no longer be valid, according to **Dr. Ian Landells**, Clinical Chief of the Division of Dermatology at Eastern Health in St. John's, Newfoundland and Labrador.

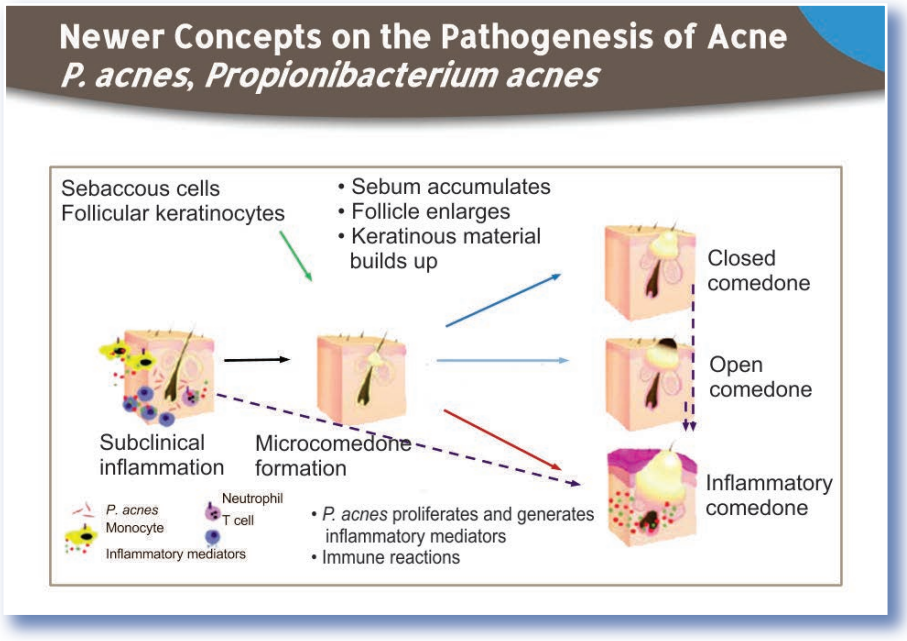
"Newer information is that the roles of pathogenic factors may be different than we previously thought," he told a symposium at Dermatology Update in Montreal. "Inflammation—the 'Big Bad Boy' of acne—may not be just the downstream result of acne.

"This publication actually shows there is sub-clinical inflammation before the formation of acne comedones, and before any evidence the inflammation is present," he said, referring to a recent edition of *Journal of Drugs in Dermatology* (2013; 12 (suppl (6):s70-272).



Classic concept

In the classic concept of inflammatory acne pathogenesis and progression, follicular hyperkeratinization is followed by microcomedone formation and abnormal desquamation, which produces a plug that upsets sebum balance and triggers an immune response. As follicular enlargement, hyperkeratinization and excess sebum production continues, the comedone develops into a non-inflammatory lesion, which may then progress to an inflammatory papule or pustule.



New concept

In this new pathologic concept, Dr. Landells explained that P. acnes interacts with monocytes and neutrophils, and proliferates to generate inflammatory mediators that result in inflammation and comedone formation.

This new concept of the development of chronic acne considers inflammation to be the result of a cascade of events, beginning with a relative deficiency of linoleic acid that culminates in very high levels of IL-1-alpha.

Sebum production is partly regulated by peroxisome proliferator-activated receptors during this cascade, and the sebaceous gland responds to stress, infection and nutritional deficiencies. Ultimately, an immune reaction is provoked with CD4-1 lymphocytes and macrophages that produce an inflammatory response.

"This has led to a new hypothetical model of how acne works," Dr. Landells said. In this scenario, P. acnes and other stimuli activate cytokine production through the nuclear factor-kappa B signalling pathway. TNF-alpha and IL-1-beta also stimulate Activator Protein 1 transcription factor signalling, driving the synthesis of matrix metalloproteinases, while IL-1-beta recruits cells such as neutrophils.

"So, we have sub-clinical inflammation internally, and a cascade that causes clinical inflammation," Dr. Landells said.

Many pro-inflammatory agents have been implicated in the development of P. acnes and acne lesions, he noted. Fatty acids, porphyrin and squalene peroxides have been identified as tissue damage factors, lipase enzyme as a chemotactic factor and heat shock proteins as stimulant factors. A number of pro-inflammatory cytokines (chemokines, interleukins, interferons) are also recognized as early response factors to the tissue damage associated with acne.

Different patterns of inflammation

"What is interesting about P. acnes—and this is a hard one to explain—is that adolescents who don't have acne, have low levels of P. acnes," Dr. Landells said. "If they do have acne, they have much, much higher levels of P. acnes: 105 organisms per cm squared.

"But with adults you don't see that difference. That might suggest, as we've seen in acute and chronic atopic dermatitis, a totally different mechanism and a totally different pattern of inflammation."

Reduction of P. acnes diminishes inflammatory byproducts

Acne vulgaris is primarily an inflammatory disease. Research confirms that all acne lesions, down to the microcomedo—the initiating lesion of acne vulgaris—are inflammatory in nature.[1,2] However, the role of P. acnes in the pathogenesis of acne vulgaris is well established. Current understanding reflects the reality that P. acnes mediators contribute directly to local inflammation in the pilosebaceous unit.[2] Therefore, although acne vulgaris is not an infectious disease, treatment aimed at the P. acnes bacteria is essential. Reduction of P. acnes colonization will diminish inflammatory byproducts.

Clindamycin's anti-inflammatory and anti-microbial activity

Evidence suggests that clindamycin, a lincosamide antibiotic frequently used for the management of acne vulgaris, has both anti-P. acnes activity and direct and indirect antiinflammatory effects.[3]

Preventing antibiotic resistance through combination therapy[4]

On the other hand, global concern about the issue of antibiotic resistance, which has been documented around the world, to P. acnes, has caused the dermatology community to reassess our use of both oral and topical antibiotics to treat acne vulgaris.[5] While resistance concerns are justified, and responsible prescribing is essential, topical clindamycin, *not* as montherapy, still retains a critical role in the management of acne patients. Used in combination with other topical agents, such as benzoyl peroxide or retinoids, topical clindamycin offers important therapeutic benefits. The addition of BPO has been shown to suppress the development of clindamycin resistant P. acnes. Therefore, it is crucial to emphasize the use of antibiotics in combination with benzoyl peroxide to prevent or reduce antibiotic resistance as part of our antimicrobial stewardship, knowing that antimicrobials play an essential role in acne.

—Dr. Leon H. Kircik, Associate Clinical Professor of Dermatology at Indiana University Medical Center in Indianapolis and Adjunct Attending in the Department of Dermatology at New York City's Mount Sinai Medical Center

1. Webster GF: The pathophysiology of acne. *Cutis* 2005 Aug; 76(2 Suppl):4-7.
2. Burkhart CN, Gottwald L: Assessment of etiologic agents in acne pathogenesis. *Skinmed* 2003 Jul-Aug; 2(4):222-228.
3. Del Rosso JQ, Schmidt NF: A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis* 2010 Jan; 85(1):15-24.
4. Leyden JJ: Effect of topical benzoyl peroxide/clindamycin versus topical clindamycin and vehicle in the reduction of Propionibacterium acnes. *Cutis* 2002 June; 69: 475-480.
5. Kinney MA, Yentzer BA, Fleischer AB Jr, Feldman SR: Trends in the treatment of acne vulgaris: Are measures being taken to avoid antimicrobial resistance? *J Drugs Dermatol* 2010 May; 9(5):519-524.

New understandings of the role of inflammation in the pathogenesis of acne

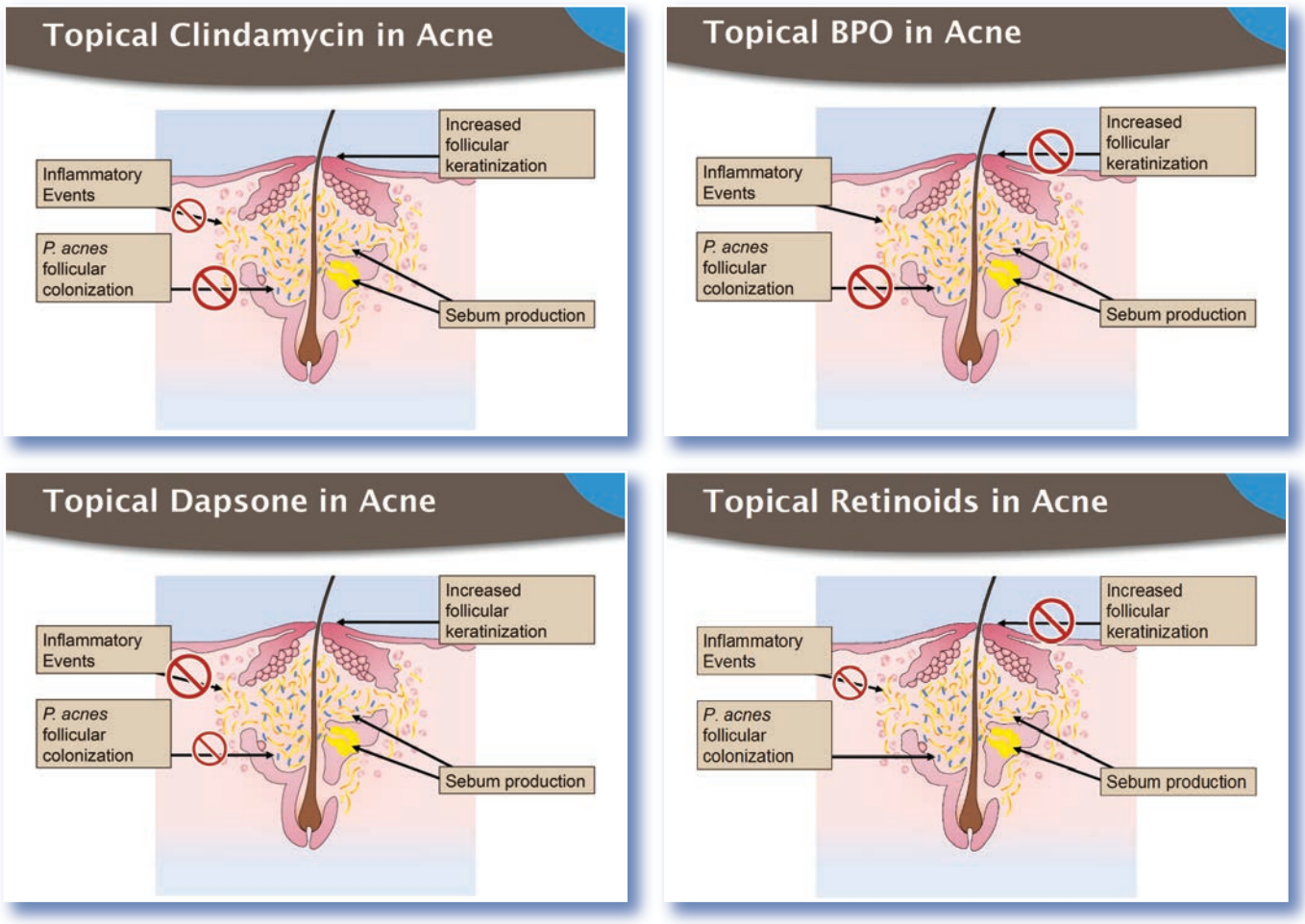
Sub-clinical inflammation could be primary event

Evidence of sub-clinical inflammation in acne vulgaris was presented more than 20 years ago, Dr. Landells noted, when one study detected bioactive IL-1-alpha-like material in 76% of supernatant open comedones, and in 58% of the cases the levels of this material exceeded 100 pg/mg (*J Invest Dermatol* 1992; 98:895-901).

Additional evidence that sub-clinical inflammation could be the primary event in acne was presented by Jeremy and colleagues in 2003, in their report that biopsy specimens of clinically normal pilosebaceous follicles with no micro-comedonal features from acne patients contained elevated CD4, T-cells, macrophages and up-regulated IL-1.

A more recent study used computer-assisted alignment and tracking to show that while most inflammatory acne lesions emerge from comedones, 28% emerge de novo (*J Am Acad Dermatol* 2008; 58:603-608).

"These were patients who did not have any active keratitis, significant papules or pustules or evidence of 'ice pick' scars," Dr. Landells reported. "These were patients who did not have any clinical evidence of inflammation.



There seems to be a process leading to the development of inflammation."

Clinical implications

Dr. Landells added that this is good evidence to support the treatment of uninvolved skin—not just visible lesions—in acne patients and may validate the topical use of anti-inflammatory-based treatments.

"It is really important to understand that inflammation is the primary event, and everything else is secondary," Dr. Landells said. "This impacts on the selection of acne treatment."

Clinicians should consider early treatment with agents that treat inflammation, such as retinoids, clindamycin and dapsone and counsel patients to treat the area, rather than just lesions.

Topical molecules and their role in managing inflammation in acne

Treating clinical and subclinical inflammation

Topical retinoids are among the medications often recommended for acne treatment, said **Dr. Jerry Tan,** Adjunct Professor at the Western University's Schulich School of Medicine and Dentistry in London, Ont. They have direct anti-inflammatory properties, including phagocytotic inhibition. Tretinoins have other features, too. They smother the release of cytotoxic nitric oxide (an important mediator of inflammatory reactions), inhibit the production of pro-inflammatory cytokines (IL-5, 6, 12) and other similar agents like leukotriene LTB4.

Clindamycin is also frequently recommended as a topical acne therapy, most often in combination regimens with agents such as BPO, Dr. Tan noted. The antibacterial effect of clindamycin, a lincosamide, weakens the viability of the P. acnes micro-organism. Its anti-inflammatory properties include the inhibition of protein synthesis and lipase production, and the reduction of free fatty acids, each of which has been determined to be an important element in the emergence of the disease.

Clindamycin's mode of action against P. acnes also eliminates the presence of many of the chemotactic and cytotoxic pro-inflammatory agents the organism produces, reducing its immunogenic potential.

Topical BPO's effect on inflammation is unknown, but it has bactericidal and keratolytic actions, Dr Tan said. It releases highly reactive oxygen species, destroys polysaccharide biofilms and relaxes the cohesiveness of the stem cell at the follicular orifice.

Sulphones, Dr. Tan noted, have a long history in medical therapy, and one of them, dapsone, has proved to be useful against various forms of acne because of its direct anti-inflammatory properties. Among other effects, topical dapsone inhibits neutrophil myeloperoxidase and eosinophil peroxidase, as well as neutrophil chemotaxis.

Dapsone also downregulates IL-8, prostaglandins, leukotrienes, TNF-alpha, and lysomal hydrolase and stymies the formation of 5-lipooxygenase products.

Dr. Tan suggested BPO, antibiotics, dapsone and photodynamic therapy were the agents of choice agents against P. acnes. Azelaic acid may also be effective, but it is not officially indicated in Canada for treatment of acne. For infundibular hyperkeratosis, the use of topical and oral retinoids, possibly aniandrogens as well as other keratolytic agents may be indicated.

When the therapeutic intent is to suppress androgens and IGF-1, antiandrogens and diet and dairy changes are considered the best approaches.

To prevent hyperkeratinization, Dr. Tan recommended retinoids, BPO, hydroxyacid and antiandrogens as the best choices. To suppress inflammation due to neutrophil phagocytosis and chemotaxis, retinoids, clindamycin and dapsone should be the front line agents.

"When it comes to innate immune response," Dr. Tan said, "much of that can be regulated by retinoids, clindamycin, or dapsone."

The future of new therapies

The role of P. acnes in acne has expanded to involve different subtypes, termed phylotypes.

"P. acnes is not just P. acnes. It is a number of different factors," he added.

Dr. Tan reported on evidence from a recent research project, which used Multilocus Sequence Typing (MLST) to analyse P. acnes isolates. The researchers found a wide distribution and differing numbers of acne phylotypes in normal skin, and skin affected by acne and other clinical conditions.

For example, the percentage of P. acnes phylotype 1A1 was 39% in normal skin, but 74% in acne. In soft tissue this phylotype approached 50%, edged above 40% in blood, and was midway between these numbers in ophthalmic conditions.[1]

"[These results] will be vitally important as we seek to develop new and specific therapeutic and diagnostic strategies for P. acnes-related diseases," the researchers concluded.

[1] *www.plosone.org/article/info:doi/10.1371/journal.pone.0070897* or *www.tinyurl.com/kvczqzr).*

Supplement to *The Chronicle of Skin & Allergy,* February 2014. Chronicle is an independent medical news service that provides educational updates regarding medical developments around the world. Views expressed are those of the participants and do not necessarily reflect those of the publisher or sponsor.

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Clinical practice

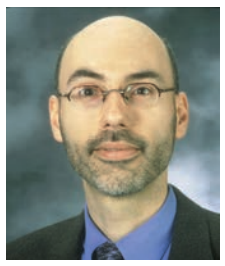
IL-23 shows unexpected behaviour

■ Unexpected cytokine expression seen in studies of ustekinumab for treatment of PPP, PPPP

by JOHN EVANS,
Assistant Editor, The Chronicle

A study into the efficacy of ustekinumab in palmo-plantar pustular psoriasis and pustulosis has found unexpected behaviour in the interleukin-23 (IL-23) signalling pathway in these conditions, according to a paper published online in the *Journal of the European Academy of Dermatology and Venereology* (Sept. 24, 2013).

While no significant improvement was seen in the 20 patients with palmo-plantar pustular psoriasis (PPPP) or the 13 with palmo-plantar pustulosis (PPP) receiving treatment with 45 mg of the anti-IL-12/IL-23 antibody ustekinumab, unexpected cytokine expression seen in assays may suggest a cause for this lack of efficacy, says Dr. Robert Bissonnette, Montreal-based dermatologist and president of Innovaderm Research, lead author of the study.



Dr. Robert Bissonnette

May have identified different mechanisms of inflammation

"The main finding, I think, of that study, and the most interesting finding in my opinion, is the fact that using PCR, we saw in untreated PPP and PPPP skin an increase in expression of IL-17A, without an increase in expression of IL-23, which is peculiar. [It's] different from what you find in plaque psoriasis, and could explain why we didn't see the efficacy," says Dr. Bissonnette.

"From a mechanistic point of view, it seems this variant of psoriasis, at least for palmo-plantar pustulosis and palmo-plantar pustular psoriasis, the mechanisms of inflammation seem to be different than for plaque psoriasis," he said.

In addition to the 33 patients with palmo-plantar disease, seven participants with normal palmo-plantar skin were also recruited. Patients received either 45 mg of ustekinumab or placebo at day zero and week 4. Those receiving the placebo were crossed over to ustekinumab at week 16. The evaluated endpoint was the number of patients treated with ustekinumab who achieved a 50% improvement on the Palmoplantar Pustular Area and Severity index (PPPASI-50) vs. placebo. Biopsies taken from the palms and soles of both patients and participants with normal skin were also analysed via RT-PCR and immunohistochemistry.

"The rationale was to try and develop better treatments for patients with palmo-plantar pustulosis, and palmo-plantar pustular psoriasis. It's a very difficult-to-treat variant of psoriasis. We don't have many treatments that have been studied specifically in that patient population, and both treatments we have don't tend to work that well," says Dr. Bissonnette. "It is one of the most devastating types of psoriasis, because when hands or feet are affected, people can't walk or function with their hands. It has a tremendous impact on quality of life."

Unusual cytokine response

Ustekinumab was chosen for the trial as the other biologics that are currently on the market are all TNF antagonists, which have been reported to induce new onset of pustular lesions in hands of patients with rheumatoid arthritis, Crohn's disease, and psoriasis, Dr. Bissonnette says, and the only other biologic available in that bracket is ustekinumab. "At the time the study was designed, there was very little knowledge on the efficacy of that product in this patient population."

The unusual cytokine response seen in these patients needs to be further studied, says Dr. Bissonnette. "Among what should be studied, I think, is trying to repeat this finding, trying to see if it is specific to pustular palmo-plantar psoriasis or also found in patients with non-pustular palmo-plantar psoriasis. Is it an issue of the area, or the type of disease?

"From the mechanistic point of view we need to understand how and why can we have such a high level of IL-17A without IL-23. IL-23 is known to be responsible to maintain the TH-17 cells."

He says he wonders if it is possible for IL-17 to be produced by another cell type. "In the literature there are suggestions that other cell types like mast cells or neutrophils could produce IL-17A. So that's one possibility.

> *"From a therapeutic point of view, this, to me, suggests that anti-IL-17A agents should be studied in that variant of psoriasis . . ."*
> *—Dr. Robert Bissonnette*

"From a therapeutic point of view, this, to me, suggests that anti-IL-17A agents should be studied in that variant of psoriasis, because of that strong IL-17A signal without IL-23. These are not yet on the market, but it will be interesting to see how efficacious they are in that type of disease."

Another study of ustekinumab in treating PPPP and PPP, carried out at approximately the same time by a different group, did show some efficacy with a larger dose, notes Dr. Bissonnette (Gottlieb AB, et al: *Journal of Dermatological Treatment* June 2013; 24(3)179-187).

"They took patients with pustular palmo-plantar psoriasis and non-pustular palmo-plantar psoriasis, and treated them with either the lower 45 mg dose or the higher 90 mg dose," he says. "What they found was that patients treated with the 45 mg dose did not improve much; however, some patients treated with 90 mg did improve. In our study, all our patients who were randomized to receive ustekinumab were treated with 45 mg.

"So my conclusion, based on those two small studies, is that for palmoplantar pustular psoriasis, ustekinumab at a dose of 45 mg doesn't work that well. Some evidence suggests that a dose of 90 mg would work better."

Non-proprietary and brand name of therapy: *ustekinumab (Stelara, Janssen).*

Clinical practice

Apps grown in number, and popularity

■ Which dermatology apps are of value, and which should you caution your patients against using?

by EMILY INNES,
Assistant Editor, The Chronicle

There are more than 200 dermatology mobile applications available across a variety of platforms, which range in purpose, price, efficacy, and even credibility, according to a study published by *JAMA Dermatology* (Nov. 2013; 149(11):1300-1304).

The study's investigators found 229 dermatology-related applications on Apple, Android, Blackberry, Nokia, and Windows, which were categorized into general dermatology reference (61 apps), self-surveillance/diagnosis (41), disease guide (39), educational aid (20), sunscreen/UV recommendation (19), calculator (12), teledermatology (eight), conference (six), journal (six), photograph storage/sharing (five), dermoscopy (two), pathology (two), and other (eight).

"The widespread variety and popularity of mobile apps demonstrate a great potential to expand the practice and delivery of dermatologic care," the study's authors wrote.

Dr. Ann Chang Brewer, with the Mayo Clinic Arizona in Phoenix and the study's lead investigator, said she did not expect to discover so many apps dedicated to the field of dermatology.

"I knew that mobile apps were really popular and that they are fairly easy to create . . . but I was surprised about the kind of variety of apps that I found," said Dr. Brewer.

The apps ranged in price from $0.99 to $139.99 with a median of $2.99 (prices in U.S. dollars), but Dr. Brewer said the price does not always dictate the quality and many of the better apps are often free.

She said one of the best apps she has used was developed after the study was published by The American Academy of Dermatology. The app has a general reference section for patients, uses GPS to find any board-certified dermatologists in the patient's area, and the UV index is determined by GPS to inform the user about how much sunscreen to apply. She recommends that her patients use sunscreen reminder apps.

Look for apps from credible organizations

"Any of the apps, when you look at the developer and you can recognize the name as a reputable organization or institution, I think those ones are fairly credible," said Dr. Brewer. "However, none of them have been approved by the [U.S.] FDA."

Dr. Brewer said one useful app for physicians is called VisualDx, which has a large photograph and reference database of skin diseases. The application allows a physician to use it to make a differential diagnosis. She said it is a good tool for clinicians, especially non-dermatologists; however, it comes with a hefty price tag. It is listed at a minimum of $199 on the iTunes website for a one-year subscription.

She said it is important to investigate whether or not the author has an ulterior motive for creating the app, such as a beauty app that might have been made with the purpose

Please turn to **Apps** page **35**→

SPECIAL REPORT

Paradigm Shift *in* Wound Healing

New consideration should be to use ingredients that do not contribute to topical antibiotic resistance and allergen exposure

While topical products containing antibiotics have commonly been used prophylactically on minor skin wounds, research does not support their use in the prevention of infection or for speeding wound healing. With concerns about the emergence of antibiotic-resistant microbes, as well as contact sensitization, effective alternatives to these products would be valuable.

As such, antibiotic-free non-allergenic products are recommended for speeding the healing of minor wounds and smoothing irritated skin.

In this Special Report, four leading Canadian dermatologists discuss different aspects of the new therapy, how it works, and the opportunities it presents for clinicians and patients.

Are topical antibiotics necessary in wound care?

Dr. Gary Sibbald

Director of Wound Healing
Women's College Hospital
Toronto

What is known about the contribution of topical agents containing antibiotics to the rise in antibiotic resistant bacteria?

The first thing that we know is that for antibiotics to become resistant, you probably only need one mutation. We generally have a rule that if we use [a medication] topically, we don't use it systemically because resistance arising from topical use [may make those antibiotics ineffective] in systemic use.

So how successful have attempts been to educate medical practitioners and the lay public regarding the potential development of antibiotic-resistant bacteria from the use of topical agents?

I think there has been some success, but not widespread success. We are trying to steer people away from topical antibiotics that might breed resistance because they are being used systemically.

The other big issue is that a lot of the topical antibiotics have become sensitizers. One of those topical antibiotics is neomycin. As a result, not only do we worry about the resistance problem, but we worry about sensitization.

What other particular concerns are there regarding allergic sensitization?

That might be a concern in atopic individuals, and/or those with eczema, who might be prone to allergic sensitization.

Regarding neomycin, in a large series from the Mayo Clinic, patients were allergic at a rate of 11.5%. In the North American Contact Dermatitis Group, it was 11.2%. It's kind of interesting though—in a recent study we conducted, we only got 4%, because for over 25 years we've discouraged our population from using neomycin.

Another common component is bacitracin. In our study, we had 8% sensitization to bacitracin. The North American Contact Dermatitis Group had 8.7%, and the Mayo clinic 9.2%. So you're getting up to what we call a common sensitizer.

Another antibiotic, polymyxin, also has shown increased sensitization potential. So all of a sudden we are looking at a population which we are sensitizing to topical antibiotics. Also, we don't really have any evidence that topical antibiotics promote wound healing.

There are a number of agents, including madecassoside which is a botanical extract that improves wound healing. There is copper, zinc, and maganese that are also pro-enzymes involved in the wound healing process, and antinol, which is also anti-inflammatory and gives a soothing and drying effect. So you've got promoters of wound healing vs. potential allergens.

Are there any allergy or sensitization concerns related to the active ingredients such as panthenol B5, madecassoside and zinc copper?

None of the active ingredients are common allergens. We performed patch tests, and tried to identify these allergens. I think it is important to distinguish eczema or dermatitis and contact dermatitis from irritation. About 80% of contact dermatitis is related to irritants such as soaps, detergents, things that are irritating to the skin, vs. about 20% that are true allergens.

Zinc and copper are known to have some antimicrobial properties. What other benefits would these ingredients have in a topical agent?

They act as antibacterials, but they also act as co-factors for enzymes that are part of the wound healing cascade. So they actually promote wound healing through an indirect way of acting as a co-factor, activating the various enzymes in wound healing.

Topical allergens can affect wound care

Dr. Sandy Skotnicki

Medical Director,
Bay Dermatology,
Toronto

What are the benefits of a healing emulsion product that is paraben-free, fragrance, and lanolin-free?

I think there is a lot more urban myth and public panic than there needs to be [about parabens], because they are very safe. They are the most widely used preservative not only in cosmetics but in foods and very rarely do they cause problems.

But fragrance should really not be in any kind of product at all, especially not in a healing product, because the skin is going to be more sensitive or irritated because it has a wound.

Fragrances are irritants as well as allergens and if you have an open sore the chances of becoming sensitized and then allergic to fragrances is higher.

Lanolin is an allergen and again we have lots of options now for emollients and moisturizers so you do not need lanolin in a healing product. However, parabens in wounds can lead to a higher percentage of allergic sensitization than on normal skin. For this reason they are never used as a preservative in wound products.

Why do patients with eczema or atopic dermatitis have to be particularly careful selecting a treatment for skin wounds?

If you have eczema or dermatitis your skin is more irritable, and the barrier is comprised.

I do not like the term sensitive skin. A lot of products use that term to entice people to use their products. [Many] products made for sensitive skin have fragrances and lanolin and all kinds of things that should not be in there—it is just a marketing term.

Fusidic acid is an antibiotic and you do not need an antibiotic on uninfected skin. Part of the problem with using bacitracin and neomycin on skin that is not infected is we are increasing bacterial resistance. We are now finding bacterial resistance not just from overuse of oral antibiotics but from overuse of topical antibiotics.

I do not recommend people put bacitracin on a sore unless they think it is infected. Bacitracin has an 8% incidence of allergic contact dermatitis in North America, so that is another reason why you should not use it unless you need it.

Why do some over-the-counter wound care treatments cause contact dermatitis in some patients, but other products do not?

Any patient can develop an allergy to a non-medicinal or even medicinal over-the-counter cream. Bacitracin is an allergen. If you use a product long enough—and allergy comes with repeat exposure—your chances of becoming allergic to it becomes higher…

Do you think this new therapy is safer for children and infants than some other wound and healing products on the market?

If you look at the ingredients, [panthenol B5, madecassoside, and zinc copper] do not have fragrance, do not have lanolin, do not have parabens, and there are no allergens—so yes.

A lot of times I recommend a product for what it does not have in it, not necessarily what it does have, and this is a paradigm shift.

Do some patients need to be concerned about potential metal allergies because of the copper, zinc, and manganese salts found in the product?

Absolutely not. The concentration is too low, the presentation of the metal to the skin can't really induce an allergy.

Assessing the literature regarding the active ingredients such as panthenol B5, madecassoside, and zinc copper

Dr. Lyn Guenther

Medical Director
Guenther Dermatology Research Centre
London, Ont.

What does the existing literature suggest about the efficacy of madecassoside for wound healing?

Madecassoside is a botanical extract iso-

lated from centella asiatica of the Apiaceae family. Studies have shown that madecassoside has anti-inflammatory and anti-oxidant properties. Topical use has been shown to enhance wound healing and heal chronic skin lesions, and increase the production and strength of collagen deposited during wound healing.

What kinds of benefits do zinc and copper contribute to wound healing, according to the latest research?

Both copper and zinc are essential trace elements. Copper is involved in hemoglobin synthesis and enzyme activation. Inflammation induces a net increase in copper in inflamed areas, in the blood, however, chronic inflammation may lead to depletion of copper stores. Copper gluconate, used topically, moisturizes the skin and decreases itching, inflammation and scaling. Zinc glutonate is an essential part of many enzymes. It is involved in protein synthesis and cell division. Topical use of zinc glutonate has been shown to support wound healing.

What are the clinical advantages of using panthenol for inflammation associated with lesions and wound healing?

Panthenol is an alcohol derivative of pantothenic acid, which is also referred to as vitamin B-5. After topical application, panthenol is rapidly converted to pantothenic acid.

Panthenol and pantothenic acid have been used for several years as a moisturizer to hydrate the stratum corneum, reduce transepidermal water loss, maintain skin softness and elasticity, and accelerate the re-epithelialization of wounds.

Dexpanthenol, the stable alcohol analogue of pantothenic acid, has been shown to suppress experimental ultraviolet-induced erythema in a dose-dependent manner, supporting its anti-inflammatory effects. Using dexpanthenol for three to four weeks has been shown to suppress skin irritation, dryness, itching, erythema, fissures, and erosion.

What advantages do these new therapies present for promoting skin healing over topical agents containing antibiotics?

Studies have shown that the use of topical antibiotics on wounds that are not infected can inhibit, rather than enhance, wound healing. This does not happen with formulations that contain panthenol B5, madecassoside, and zinc copper, which promote wound healing.

Topical antibiotics can also induce acute allergic contact dermatitis, and may be associated with bacterial resistance. Since [this new therapy] is not an antibiotic, antibiotic resistance does not occur.

How does the safety data on these ingredients compare to other topical agents used for wound healing?

These ingredients can be safely applied to both face and body in adults, children and babies. An observational study of 2,440 patients treated twice daily with a formulation containing panthenol B5, madecassoside, and zinc copper, paraben-free, fragrance-free and lanolin-free for 16 days for minor burns, fissures, rough patches, and after laser and cryotherapy, showed that the product was well tolerated. In this study, 49% of patients had lesions on the face—a region that is often sensitive.

This type of formulation is well tolerated in patients with sensitive skin, and those with inflammatory skin conditions such as atopic dermatitis. It is paraben-free, fragrance-free, and lanolin-free. It is well tolerated with minimal risk of skin irritation or contact sensitization.

For what sort of skin wounds, lesions, and conditions does the literature suggest this new therapy would be recommended, and how do you recommend it in your own practice?

Panthenol B5, madecassoside, and zinc copper are widely used in Europe to moisturize dry, scaly, itchy skin, and enhance healing after laser treatment and minor skin burns, such as those secondary to radiation therapy.

The study of laser wounds noted 25% acceleration in wound healing with a formulation containing panthenol B5, madecassoside, and zinc copper. This should be applied twice daily. I use it on fissures, particularly those that are periungual and related to frequent hand washing and excess dryness in the winter.

It's also been used in perianal fissures, and those associated with vulgar lichen sclerosis. It is very soothing to patients with dermatitis who are intolerant of many topical agents such as patients with atopic dermatitis, hand dermatitis, and diaper rash.

It can also be used in a variety of wounds, including skin abrasions, diabetic and leg ulcers, wounds created after electrodessication and curettage, and laser. It is also helpful to heal ruptured blisters such as the ones we see with dermal burns or after cryotherapy for actinic keratosis, or blistering conditions such as bullous pemphigoid.

It can help restore barrier function and decrease transepidermal water loss. So the potential is extremely huge for what this product can do.

Poster data presented at the EADV sessions

Dr. Charles Lynde
Director of the
Lynde Centre for Dermatology
Markham, Ont.

Why do you think the combination of panthenol, madecassoside, and copper/zinc/manganese salts had such a high reported tolerance and satisfaction rating of "excellent" or "good" (98% and 96% respectively) in this clinical trial of 2.440 patients (Crickx B, Lacour JP, Arsan A, et al: A French Observational Study on the Management of Epidermal Wound Healing. Poster presentation, EADV Oct. 2013, Istanbul, Turkey)?

Formulations that contain panthenol B5, madecassoside, and zinc copper, and that are paraben-free, fragrance-free and lanolin-free have the ability for calming and repairing the skin. It includes a number of ingredients such as copper, zinc, and magnesium, which have all been known to be able to repair damage to epidermal skin. They combined that with the botanical, madecassoside, which is from a plant that has been known for many years to treat skin inflammation and combined that further with some dexpanthenol, which is stable alcohol of pantothenic acid.

Why is this type of formulation able to significantly reduce burning, tingling, pain, and itching, as well as erythema, dryness, and cracking of the skin?

Panthenol basically acts on inflammatory mechanisms and reduces skin homeostasis. We know that madecassoside normalizes skin re-epithelialization and the copper, zinc, and magnesium have antibacterial properties.

The exciting thing about this particular type of formulation is that it is a paradigm shift. [Often when patients] come in with abrasions or cuts, most family doctors and sometimes dermatologists use topical antibiotics that might have neomycin or [polymyxin bacitrain]. These can cause sensitization, contact dermatitis and promote antibiotic resistance.

How do these results compare to other healing emulsion products on the market in Canada?

Far better. You do not have the problems of sensitization, allergic contact dermatitis, or antibiotic resistance. They heal wounds without irritation and people find them soothing.

The study included a large range of epidermal lesions. How do these types of formulations address such a wide range?

They are used for quite a wide range, treating anything that produces epidermal barrier dysfunction and problems, such as burns, grazes, superficial wounds, little lacerations, small areas of dermatitis, dry skin spots. This extends all the way through from babies to adults to geriatrics.

I see them eventually being used after skin biopsies, or after a number of small surgeries performed by dermatologists, to promote skin healing.

At the present time, petroleum jelly is often used and it is just a bland, occlusive dressing. It does not have any true healing properties, or anything that calms or repairs the skin, it is just purely occlusive.

What are your impressions regarding the effectiveness of the formulation used in this study? In what clinical situations would you recommend it to your patients?

The study has shown quite a range of effectiveness in many of the different minor skin issues that we deal with. That includes, as I mentioned, small burns, small irritation of the skin, small cuts, atopic dermatitis that is not healing, and after surgeries we use it after we do biopsies after the area heals. I have quite a number of people that have used this product already, and I get quite positive results.

We use a lot of liquid nitrogen for warts and small skin cancers, and we are about to start a small study looking at using such a type of formulation post cryotherapy to help heal the area more quickly.

Traditional topical products used by dermatologists in the aftercare of patients treated with cryosurgery for actinic keratosis may inhibit wound healing, contribute to the development of antibiotic resistance, and lead to allergic sensitization.

According to a survey of Canadian dermatologists conducted in Dec. 2013, of those who reported applying a topical after performing cryosurgery, Petrolatum was most commonly selected by 66.67%, followed by fusidic acid and bacitracin. For at-home use by the patient, the clinicians recommended petrolatum (86.36%), bacitracin (45.45%) and fusidic acid (31.82%). Several studies have noted that petrolatum may contribute to allergenicity, inhibit wound healing, and lead to poor scarring.[1,2,3]

The online survey of eight questions was sent to 321 dermatologists, with 84 (26.2%) responding.

1. Sheth VM, et al: North American Contact Dermatitis Group 2008; 19(4):181-189.
2. Jia S, et al: Wounds 2011; 23(6):160-165.
3. Kircik LH: J Drugs Dermatol 2013; 12(1):86-90.

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Transgenic skin cells shown effective at 6-1/2 year follow-up

A LONG-TERM FOLLOW-UP of the utilization of gene therapy for the treatment of human skin disease has shown lasting benefits, according to research published online in *Stem Cell Reports* (Dec. 26, 2013).

The research followed up results six and a half years after trial completion with the single participant of a Phase I/II clinical trial of autologous genetically modified cultured epidermal stem cells for gene thereapy of junctional epidermolysis bullosa. Epidermal keratinocytes on the subject's palms were found to contain an appropriate number of holoclones, and were sampled and modified ex vivo before being re-implanted into prepared sites on the upper leg. Synthesis of normal levels of laminin 332 were seen in the graft sites, along with the development of firmly adherent epidermis—stable at one year follow-up without blisters, infections, inflammation, or immune response. At the 6.5 year follow-up, the experimental regions of skin on the subject's upper thighs retained normal appearance without itching or blistering, with the transgenic epidermis being fully functional and nearly indistinguishable from normal epidermis. While the majority of the transduced keratinocytes were lost within a few months of grafting, the epidermis in the area was supported by long-lasting, self-renewing transgenic stem cells. The authors suggest their results open the door to safe use of epidermal stem cells in combined cell/gene therapy for genetic skin diseases.

—**For more information visit http://tinyurl.com/kgvam2f**

How MRSA strain USA300 developed resistance to antibiotics so quickly

AN INTERNATIONAL TEAM OF RESEARCHERS say they have identified the means by which methicillin-resistant Staphylococcus aureus (MRSA) strain USA300 was able to so quickly develop its resistance to antibiotics, according to a paper published in *mBio* (Dec. 17, 2013; 4(6):e00889-13).

The authors note that the USA300 lineage of methicillin-resistant S. aureus (MRSA) expanded extremely rapidly across the U.S., beginning in the late 1990s, supplanting many other S. aureus strains. Within S. aureus, the largest genomic region that distinguishes MRSA from other strains of S. aureus is the arginine catabolic mobile element (ACME).

According to the research, segments of ACME were originally assembled into one genetic region within Staphylococcus epidermis (S. epidermis), this then underwent horizontal transfer to the common ancestor of the USA300 strains. One gene within ACME, speG, gave USA300 the ability to withstand levels of skin-produced polyamines such as spermidine which are toxic to related S. aureus strains. This tolerance to polyamine, mediated by speG, was also observed to enhance biofilm formation, adherence to fibrinogen and fibronectin, and resistance to antibiotic and keratinocyte-mediated killing.

The authors suggest that these traits gave USA300 a selective infection and colonization advantage, contributing to its success and allowing it to replace other, less-virulent S. aureus strains.

—**For more information visit http://tinyurl.com/lzgobqx**

Study investigates metabolic syndrome and cardiovascular disease in children with psoriasis

FINDINGS INDICATE THAT CHILDREN WITH PSORIASIS should be evaluated for components of metabolic syndrome (MetS) in order to prevent future cardiovascular disease (CVD) morbidity and mortality, researchers report in a study published in a recent issue of *Pediatric Dermatology* (Nov/Dec 2013; 30(6):700-705).

The authors note that while adults with psoriasis are known to have a greater risk of developing MetS and CVD, there have been few studies into the prevalence of MetS and other CVD risk factors in children with psoriasis. They carried out an assessor-blinded study of 20 children aged between nine and 17 years. Participants had a current or previously documented history of psoriasis involving 5% or more of their body surface area, or psoriatic arthritis. They were compared with a cohort of age-and sex-matched controls with benign nevi, warts, or acne. The primary endpoint, MetS, was defined for this study by the presence of abnormal values in at least three of the checked measures—triglycerides, high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), waist circumference, and blood pressure. Other endpoints included C-reactive protein (hs-CRP), total cholestorol (TC), and low-density liporotein cholesterol (LDL-C). Among the children with psoriasis, 30% (six of 20) met the MetS criteria. Only 5% (one of 20) in the control group met these criteria. The children with psoriasis also had higher mean FBG than the controls (91.1 mg/dL vs 92.9 mg/dL, p=0.01). However, there was no significant differences in the other four components of MetS, BMI, BMI percentile, hs-CRP, TC, or LDL-C.

—**For more information visit http://tinyurl.com/qxvhv74**

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Practical Therapeutics and Clinical News from the World of Dermatology ■ February 2014

Advances in dermatologic care in 2014

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Research

Small molecules seen as next advance in psoriasis therapy

■ Oral biologic may be helpful for patients reluctant to receive injections

by Lorrie Gagnon, Correspondent, The Chronicle

Clinical practice

New topical for herpes labialis approved for use in Canada

■ Important to initiate new therapy at first sign of prodrome

Dr. Gary Sibbald

Diagnosis

Cellulitis cases hospitalized more frequently, for longer, in Canada

■ More training, dermatology consults required to prevent misdiagnosis of cases

by Emily Isaiss, Assistant Editor, The Chronicle

The Chronicle of SKIN & ALLERGY

Advances: *Formulations for accurate isotretinoin dosing*

Continued from page 18

source of allergy, noted Dr. DeKoven, but there is no consensus on the conditions under which an implant should be removed.

"We are being inundated to patch test people pre- and post-surgery," said Dr. DeKoven. "However, it is not definitively known whether there is a causal relationship between sensitization to nickel/cobalt and a subsequent joint implant failure or whether the sensitization occurs merely as a consequence of nickel/cobalt release from a failing joint secondary to a general inflammatory reaction. The presence of a localized dermatitis occurring over the site of a joint replacement may be a sign of metal contact allergy but having a focal contact dermatitis may not be a reason to remove an implant that is working properly."

The release of a foam formulation of minoxidil that is applied once-daily is appreciated by patients.

"It's not as greasy as the liquid," says Dr. Jeff Donovan, a Toronto dermatologist, hair transplant surgeon, and assistant professor at the University of Toronto. "There is greater cosmetic acceptability of this application. The other advantage is that the foam formulation doesn't contain propylene glycol. Propylene glycol, which is in the liquid formulation, gives a certain proportion of people pruritus."

New isotretinoin formulation

A new formulation of isotretinoin permits flexible weight-based dosing, observes Dr. Marlene Tan Dytoc, a dermatologist in Edmonton and clinical professor of medicine at the University of Alberta in Edmonton.

"The capsules come in 10, 20, 30, and 40 mg," explains Dr. Dytoc.

Another key advantage is that patients don't have to eat a high-fat diet to optimize the medication, as was recommended for the original formulation.

"[The new formulation] allows for better absorption," says Dr. Dytoc. "The patients don't need to consume a high-fat meal to take it."

The PicoSure Laser has demonstrated great efficacy in removing tattoos, and dermatologists like Dr. Metelitsa are finding that the technology has other applications.

"Very early work is showing that the Picosecond technology is also helpful in terms of photorejuvenation for patients," said Dr. Metelitsa. "It appears that there are numerous applications [for the Picosecond technology]."

Hidradenitis suppurativa

In recent years, there have been no breakthroughs in the treatment of hidradenitis suppurativa, but adalimumab is now being studied as a therapy for the chronic disease, noted Dr. Landells.

Data presented at last year's congress of the European Academy of Dermatology and Venereology highlighted Phase II results with adalimumab in the treatment of patients with moderate-to-severe hidradenitis suppurativa. The biologic showed a significant reduction in abscess and inflammatory nodules from baseline. Phase III trials are ongoing.

"That [adalimumab] is something we hope in the future will be approved [to treat hidradenitis suppurativa]," said Dr. Landells.

Another biologic, omalizumab, is a breakthrough for patients with chronic urticaria, says Dr. Landells.

"I have started prescribing it to patients," said Dr. Landells. "The data behind it are solid, and the patient response has been very good."

A study published in Jan. 2014 looked at the success with retreatment of omalizumab in patients with recurrence of chronic urticaria symptoms and found all patients experienced complete response after retreatment (*JAMA Dermatology* 2014; Jan 29).

Non-proprietary and brand names of therapies: *ustekinumab (Stelara, Janssen); efinaconazole 10% topical solution (Julia, Valeant); acyclovir 5% and hydrocortisone 1% (Xerese, Valeant); doxycycline monohydrate 40 mg capsules (Apprilon, Galderma); adalimumab (Humira, Abbvie); omalizumab (Xolair, Novartis); minoxidil, Rogaine Foam 5%, Johnson & Johnson); isotretinoin (Epuris, Cipher).*

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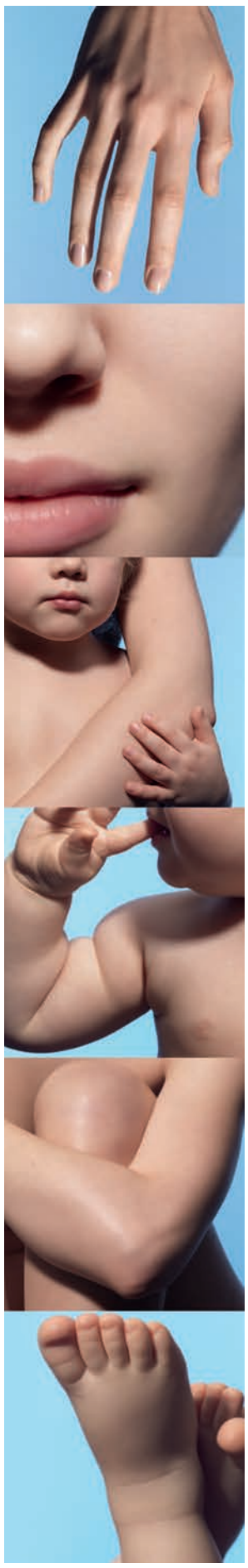

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Chronicle POSTGRADUATE EDUCATIONAL SUPPLEMENT

Prevalence, incidence and predictive factors for hand eczema in young adults—a follow-up study

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ABSTRACT

Background: Hand eczema is common in the general population and affects women twice as often as men. It is also the most frequent occupational skin disease. The economic consequences are considerable for society and for the affected individuals.

Methods: To investigate the prevalence and incidence of hand eczema and to evaluate risk factors for development of hand eczema in young adults. This is a prospective follow-up study of 2,403 young adults, 16 to 19 years old in 1995 and aged 29 to 32 years, 13 years later, in 2008. They completed a postal questionnaire that included questions regarding one-year prevalence of hand eczema, childhood eczema, asthma, rhino-conjunctivitis and factors considered to affect hand eczema such as hand-washing, washing and cleaning, cooking, taking care of small children and usage of moisturisers. These factors were evaluated with the multinominal logistic regression analysis.

Results: The one-year prevalence of hand eczema was 15.8% (females 20.3% and males 10.0%, $p<0.001$). The incidence was 11.6 cases per 1,000 person-years (females 14.3 and males 5.2, $p<0.001$). Childhood eczema was the most important risk factor for hand eczema. The odds ratios were 13.17 when having hand eczema in 1995 and 2008 compared to 5.17 in 2008 ($p<0.001$). A high frequency of hand washing was important in predicting hand eczema only when having one-year prevalence 2008, OR 1.02 ($p=0.038$).

Conclusions: After 13 years an increased one-year prevalence of hand eczema was found. The significant risk factors for hand eczema changed over time from endogenous to exogenous factors.

BACKGROUND

Hand eczema is common in the general population. In a recent review of studies in the general population from mostly European countries, the one-year prevalence rates ranged from 6.5% to 17.5%.[1] Hand eczema is 1.5 to 2 times more common in females compared with males.[2,3] Swedish estimates of one-year prevalence of hand eczema in different age-groups have varied from 6.5% to 11.8%.[4-6] Among Swedish 20 to 29 year-olds, the one-year prevalence of hand eczema was reported to range from 7.5% to 10.8%.[3,4] Furthermore, hand eczema is the most common occupational skin disease.[7]

Occupation-related hand eczema has many negative consequences. The economic costs are considerable for affected individuals and for society.[8,9] Hand eczema has been shown to have an unfavourable long-term prognosis[10] and to impair quality of life.[11] These consequences could be reduced by identifying and preventing risk factors

Several exogenous risk factors for hand eczema have been reported: occupational exposure, use of detergents and wet work at home.[4,12-14] The identification and evaluation of risk factors for the development and persistence of hand eczema are important especially among young adults. During this period of life, type of occupation, household work and childcare are factors that are important to study because they might be related to the development of hand eczema. Taken together, these circumstances justify follow-up studies in early adulthood

The aim of the present study was to investigate the prevalence and cumulative incidence of hand eczema and to evaluate factors that can influence the development and recurrence of hand eczema in young adults

METHODS

Study group

This is the 13-year prospective follow-up study of a cohort of pupils in upper secondary school, 16 to 19 years old at the baseline assessment, and consequently they were 29 to 32 years old at follow-up. In 1995, 2,572 pupils in the four secondary schools in Växjö completed a self-administrated questionnaire regarding hand eczema, the response rate was 98.6%. Växjö is a town in southern Sweden with approximately 70,000 inhabitants.[15,16] In 1995, 74% of 16 to 19 year-olds attended secondary school in the study area, which was consistent with the overall attendance rate in Sweden. The 13-year follow-up of this cohort was performed in 2008. At both occasions the questionnaire was mailed in spring time. Swedish personal identification numbers were used to get updated addresses from the Swedish Population Address Register (SPAR). Addresses were found for 2,403 of the original 2,572 participants (Figure 1); 169 were unreachable: 106 had personal identification numbers not matching the SPAR register, 35 had emigrated, 21 had moved without providing a forwarding address, five were deceased, and two were not traceable for reasons of secrecy.

Questionnaire

In 1995 the questionnaire was based on the Toulihampi questionnaire.[17] The questionnaire in 2008 was based on the Nordic Occupational Skin Questionnaire 2002 (NOSQ-2002).[18] The questions regarding hand eczema were almost the same in the two questionnaires and the answer alternatives were exactly the same. Some additional questions constructed by the investigators were included in the 2008 questionnaire (see Additional file 1).

Topics surveyed by the questionnaire were: hand eczema, childhood eczema, asthma and rhino-conjunctivitis, household size and family structure, occupation and everyday activities, hand washing and skin care.

Distribution of the questionnaire

A self-administrated postal questionnaire and a pre-paid return envelope were distributed in late May 2008. A postcard was sent at the beginning of June as a first reminder. At the end of August, a second reminder was sent which included a copy of the questionnaire, a pencil and a pre-paid return envelope. Finally, a postcard was sent in the middle of September as a third and final reminder.

Data analysis and statistics

One-year prevalence of hand eczema was estimated from reported hand eczema at present or having had hand eczema some time during the last 12 months (See Additional file 1). The question regarding the one-year prevalence was previously validated.[19,20] The question on point prevalence was validated, and sensitivity (73%) and specificity (99%) were calculated.[15] To estimate the true one-year prevalence for this cohort, a calculation of the one-year prevalence in relation to sensitivity and specificity was made by using the following formula: $P=(P^*+(\text{specificity}-1))/(\text{sensitivity}+(\text{specificity}-1))$. P is the estimated true one-year prevalence in the population and P* is the one-year prevalence in the sample.[5,15,21]

The cumulative incidence was calculated on the individuals reporting having one-year prevalence or ever having had hand eczema 2008 minus those who had one-year prevalence or ever had had hand eczema in 1995. The cumulative incidence is presented as the percentage of new cases of hand eczema in the cohort. Incidence rate is presented as new cases per 1,000 person-years, i.e., the cumulative incidence/13 years × 1000.

Four groups were constructed with the intention to analyse risk factors and the development of hand eczema over time. The groups were

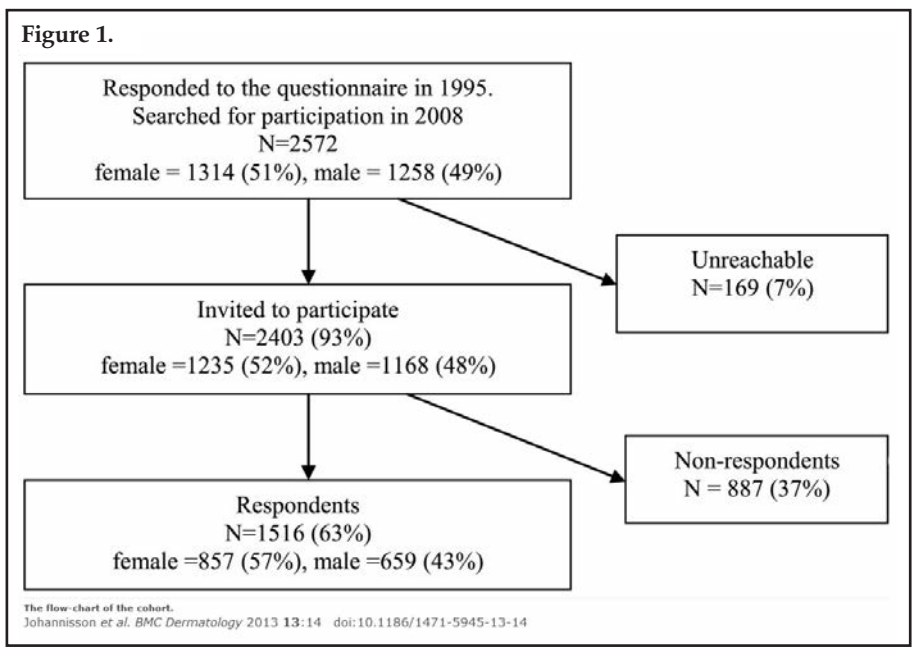


Figure 1. The flow-chart of the cohort.
Johannisson *et al. BMC Dermatology* 2013 **13**:14 doi:10.1186/1471-5945-13-14

Additional File 1: Questions from the questionnaire 2008

Year of birth: 19___ Male ☐ Female ☐

Number of persons in the household, yourself included? _____
Number of children 0 - 4 years of age? _____

How many hours a day do you usually spend:
- cook _____ *(hours)*
- cleaning/washing laundry _____ *(hours)*
- taking care of children 0 – 4 years _____ *(hours)*

How many hours a week on average have you done the following in the last 12 month?
- gardening (during summer season):_____ *(hours)*
- repairing cars/engines: _____*(hours)*
- building work, restoration: _____*(hours)*
- sports/athletics: ____*(hours*) **What kind**?_____
- hobbies: ____*(hours*) **What kind**?_____

What is your profession? _____ **Since when?** _____ *(year)*

What are your main working tasks?
_____**Since when?** ____ *(year)*

Number of working hours at ordinary work? _____*(hours/week)*

Number of working hours at additional work? _____ (*hours/week*)

Number of times a day washing hands? **At home**:_____Times/day **At work**:_____ Times/day

Did you have eczema in your childhood? yes ☐ no ☐ I do not know ☐

Have you ever had asthma? yes ☐ no ☐ I do not know ☐

Have you ever had allergic symptoms in your nose or eyes? yes ☐ no ☐ I do not know ☐

How often do you use moisturisers?

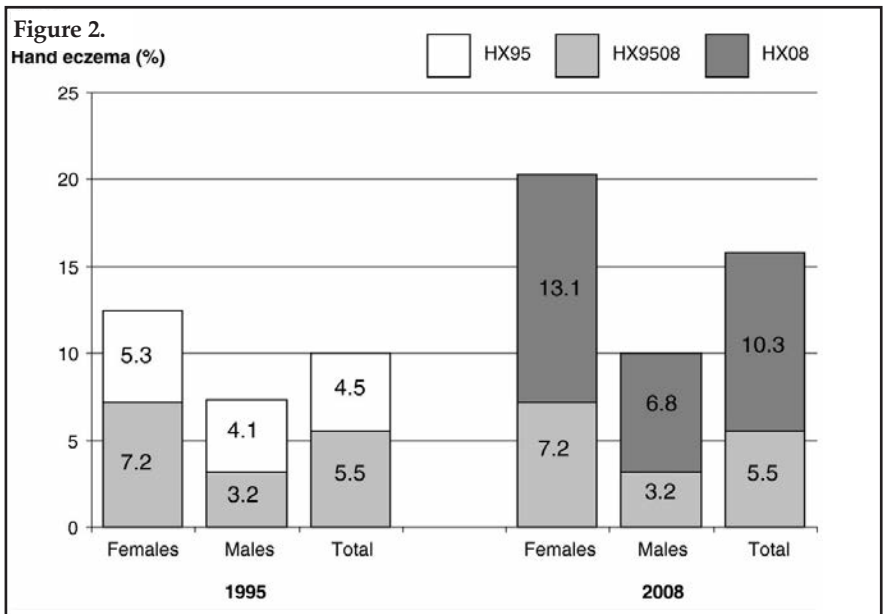
daily ☐ some time each week ☐ some time each month ☐ never ☐

How many hours a day do you use protective gloves? _____ (hours)

Have you ever had hand eczema? yes ☐ no ☐ I do not know ☐

When did you have hand eczema?
- I have it at the moment ☐
- not now, but within the last three month ☐
- 3-12 month ago ☐
- more than 12 month ago ☐

Figure 2.



The proportions reporting hand eczema in 1995 but not 2008 (HX95), both 1995 and 2008 (HX9508), and only 2008 (HX08).

constructed as follows: those who reported having a one-year-prevalence in 1995 and in 2008 are in group HX9508, those who reported having a one-year-prevalence in 1995 but not in 2008 are in group HX95, those who reported having a one-year-prevalence in 2008 but not in 1995 are in group HX08, and those who reported that they never had hand eczema are in group NoHX.

The reliability over time of self-reported childhood eczema in 1995 and then reporting the same in 2008 was determined by calculating positive predictive value (PPV); i.e., the percentage positive agreement in 2008 among the yes-respondents from 1995. The negative predictive value (NPV); i.e., the agreement of no-answers in 1995 and 2008, was also calculated.

Potential exogenous risk factors for developing hand eczema such as household size, time required for household work, frequency of hand washing, skin protective habits, working hours outside home and leisure activities were investigated by dividing the cohort into two groups. The respondents who had one-year prevalence of hand eczema 2008, i.e., the merged groups HX9508 and HX08, denominated the HX group, and the group that reported never having had hand eczema, the NoHX group. Furthermore, hand eczema was also studied in the two hand eczema groups separately regarding these factors.

Regarding occupation, the respondents were asked not only to tell their profession, but also to give information about work tasks.

The groups HX9508, HX95 and HX08 were compared to the group NoHX using a multinominal logistic regression model. The endogenous factors childhood eczema, asthma and rhino-conjunctivitis as reported in 2008 were used. The response choices in this calculation were Yes/No. Exogenous factors such as hand-washing (times a day), usage of moisturisers (dichotomized Daily/Some time each week, some time each month, never), cooking, cleaning/washing laundry, and taking care of children 0 to 4 years of age (hours a day) were investigated.

Categorical data were presented as numbers and/or proportions in groups; quantitative data were presented by mean, median and quartiles. Nominal data were tested with the Chi-squared test. When the number of expected values was insufficient, Fisher' s exact test was used. When comparing groups over time, McNemar' s test was used. Ordinal and interval data were tested with Kruskal-Wallis H-test and Mann–Whitney U-test in independent group comparisons. In the multinominal logistic regression analysis odds-ratios, 95% confidence intervals and p-values were given for all the covariates. If data was missing for any covariate, the individual was not included in the analysis. A p-value of <0.05 was considered significant in all calculations. All statistical analyses were performed with SPSS 20.0 for Windows.

Ethics

The study was approved by the The Regional Ethical Review Board in Lund, (application no 156/2008).

RESULTS

The flow-chart of the cohort is shown in Figure 1. Out of the 2,403 participants from the original cohort who received a questionnaire in the mail, 1,516 responded to the questionnaire, which was a response rate of 63%; 56% of the respondents were females. Significantly more females than males answered the questionnaire, 69.4% of the reachable original female cohort and 56.4% of the males ($p<0.001$). However, in 2008 there were no significant differences between the respondents and non-respondents in reporting one-year prevalence of hand eczema in 1995 ($p=0.677$). No significant differences were found within the genders in reported hand eczema in 1995 (females, $p=0.490$; males, $p=0.297$).

In the first dispatch, 899 (37%) responded, the first postcard reminder yielded 158 (10%) responses. On the second reminder 437 (32%) responded. With the final postcard reminder, 22 (2%) responded, which left 887 non-respondents.

One-year prevalence of hand eczema

The one-year prevalence of hand eczema in 2008 was 15.8%, Figure 2; females reported hand eczema twice as often as males, 20.3% versus 10.0%, ($p<0.001$). The estimated true one-year prevalence for this cohort was: $(0.158+(0.99-1))/(0.73+(0.99-1))=20.6\%$, 26.8% for females and 12.5% for males.The 1,516 participants were allocated to any of the four groups as previously defined; HX9508 (83/1516, 5.5%, 7.2% females and 3.2% males), HX95 (71/1516, 4.7%; 5.6% females and 3.5% males), HX08 (157/1516, 10.4%; 13.1% females and 6.8% males) and NoHX (1016/1516, 67.0%; 61.4% females and 74.4% males). One hundred and sixty respondents (10.6%) reported that they had had hand eczema at some time, but not in 1995 nor in 2008, 29 individuals, 1.9%, did not answer the question. The higher proportion of females compared with males in the hand eczema groups compared with the NoHX group was significant ($p<0.001$).

Incidence of hand eczema

In 1995, in total 13.3% (202/1516) reported they had or had had hand eczema, 139 females, (16.2%) and 63 males (9.6%), $p<0.001$. In 2008, an additional 198 individuals reported themselves having or having had hand eczema. Thus the cumulative incidence over the 13 years was 15.1% (198/1,314), for the females 18.6% and for the males 10.7%, $p<0.001$. The incidence rate was estimated as 11.6 cases per 1,000 person-years, 14.3 for females and 5.2 for males ($p<0.001$).

Hand eczema versus childhood eczema, asthma, rhino-conjunctivitis and gender

Childhood eczema was reported by 400/1,516 (26.4%) of the participants. The proportions of having had childhood eczema, asthma and rhino-conjunctivitis in the four groups in total and by gender for 2008 are shown in Table 1. The proportions of the individuals reporting only childhood eczema; i.e. not in combination with asthma and/or rhino-conjunctivitis (146/1,516, 9.6%), were found to be: HX9508, 73.9%; HX95, 41.7%, HX08, 45.5% and NoHX, 17.3% ($p<0.001$). Only having had asthma was reported by 22/1,516 (1.5%); within the groups: 1, 1, 0 and 20 individuals respectively, ($p=0.366$). Only having had rhino-conjunctivitis was reported by 201/1,516 (13.3%). Within the groups 4, 7, 11 and 179 individuals, respectively ($p=0.124$).

Self-reported childhood eczema in 2008 compared to 1995

The question about childhood eczema was answered by 1,323 of the 1,516 respondents (87.3%) in 2008. In 1995, 297/1,323 individuals (22.4%) reported childhood eczema, and 239 of these gave the same answer in 2008. This gives the positive predictive value (PPV) of 80.5% (239/297). The negative predictive value (NPV), i.e., reporting not having had childhood eczema in 1995 as well as in 2008, was 76.7% (610/795). When comparing genders, the PPV for females was 82.3% and the NPV was 77.0%. The PPV for males was 75.6% and the NPV was

Table 1

Prevalence of self-reported childhood eczema and/or asthma and/or rhino-conjunctivitis in 2008 with respect to 1-year prevalence of hand eczema and gender in the groups HX9508 (1-year prevalence of hand eczema 1995 and 2008), HX95 (1-year prevalence of hand eczema only 1995), HX08 (1-year prevalence of hand eczema only 2008) and NoHX (never having had hand eczema)

The 2008 questionnaire	Group HX9508			Group HX95			Group HX08			Group NoHX		
"Did you have eczema in your childhood?" (n = 1325, 100%)	**Females n (%)**	**Males n (%)**	**Total n (%)**	**Females n (%)**	**Males n (%)**	**Total n (%)**	**Females n (%)**	**Males n (%)**	**Total n (%)**	**Females n (%)**	**Males n (%)**	**Total n (%)**
"No" (n = 792, 59.8%)	10 (16.1)	3 (14.3)	13 (15.7)	19 (39.6)	6 (27.3)	25 (35.7)	38 (33.9)	14 (31.1)	52 (33.1)	349 (66.5)	353 (72.0)	702 (69.2)
"Yes" (n = 400, 30.2%)	48 (77.4) **a>**	15 (71.4) **a>**	63 (75.9) **b>**	22 (45.8) **a>**	14 (63.6) **a>**	36 (51.4) **b>**	63 (56.3) **a>**	23 (51.1) **a>**	86 (54.8) **b>**	140 (26.7) **a<, c>**	75 (15.3) **a<**	215 (21.2) **b<**
"I do not know" (n = 133, 10.0%)	4 (6.5)	3 (14.3)	7 (8.4)	7 (14.6)	2 (9.1)	9 (12.9)	11 (9.8)	8 (17.8)	19 (12.1)	36 (6.9)	62 (12.7)	98 (6.6)
"Have you ever had asthma?"(n = 1326)												
"No" (n = 1082, 81.6%)	37 (59.7)	15 (71.4)	52 (62.7)	38 (79.2)	19 (86.4)	57 (81.4)	84 (75.0)	35 (77.8)	119 (75.8)	433 (82.3)	421 (85.9)	854 (84.0)
"Yes" (n = 217, 16.4%)	23 (37.1)	6 (28.6)	29 (34.9) **b>**	8 (16.7)	2 (9.1)	10 (14.3) **b<**	23 (20.5)	10 (22.2)	33 (21.0) **b>**	84 (16.0)	61 (12.4)	145 (14.3) **b<**
"I do not know" (n = 27, 2.0%)	2 (3.2)	0	2 (2.4)	2 (4.2)	1 (4.5)	3 (4.3)	5 (4.5)	0	5 (3.2)	9 (1.7)	8 (1.6)	17 (1.7)
"Have you ever had allergic symptoms from your nose or eyes?" (n = 1306)												
"No" (n = 664, 50.8%)	20 (32.3)	5 (25.0)	25 (30.5)	26 (54.2)	11 (52.4)	37 (53.6)	41 (36.9)	16 (36.4)	57 (36.3)	280 (54.2)	265 (54.9)	545 (54.5)
"Yes" (n = 582, 44.6%)	40 (64.5) **a>**	15 (75.0) **a>**	55 (67.1) **b>**	21 (43.8) **a<**	10 (47.6) **a<**	31 (44.9) **b<**	63 (56.8) **a<**	24 (54.5) **a<**	87 (55.4) **b>**	211 (40.8) **a<**	198 (41.0) **a<**	409 (40.9) **b<**
"I do not know" (n = 60, 4.6%)	2 (3.2)	0	2 (2.4)	1 (2.1)	0	1 (1.5)	7 (6.3)	4 (9.1)	13 (8.3)	26 (5.0)	20 (4.1)	46 (4.6)

Significant differences ($p<0.05$) between groups, totals and/or genders are **marked with bold letters. a:** significant differences within females or within males in different groups, **b:** significant difference between totals, **c:** significant difference between females and males in a group, **<** or **>:** the group or the gender has significantly lower or significantly higher frequency than the compared group. Chi-squared test.

76.5%. There were significant differences within three of the four groups between PPV and NPV; HX9508 group: PPV=90.6% and NPV=35.0% (p=0.016); HX95 group: PPV=76.7% and NPV=60.7% (p?=?0.611); HX08 group: PPV=94.0% and NPV=55.3% (p<0.001); NoHX group: PPV=73.8% and NPV=77.6% (p<0.001).

Hand eczema and exogenous factors

The results regarding potential exogenous risk factors for developing hand eczema are shown in Table 2. The individuals in the HX group reported a significantly higher frequency of hand washing compared to the NoHX group, mean 15.4 versus 11.7 times per day (p<0.001). The females in the HX group had a significantly higher number of daily hand washing compared to the females in the NoHX-group, 17.4 versus 14.5 times per day (p<0.001).

Concerning skin care, daily use of moisturisers was reported by 60.5% in the HX group (females 67.6% males 41.5%), and by 30.6% in the NoHX group (females 47.4% and males 12.7%). The differences were significant between the two groups and between the genders within the groups (p<0.001). Regardless of hand eczema, females used moisturisers significantly more often than males; 52.9% female versus 16.2% male daily users (p<0.001), However, having hand eczema raised the reported usage of moisturizers by a factor 1.4 for females and 3.3 for males.

The exogenous factors were analysed between all four groups, in total as well as between genders (HX9508, HX95, HX08 and NoHX) and within genders in all groups, Table 3. In total as well as within females, the HX08 group had a significantly higher frequency of hand washing at home and at work than the NoHX group (p<0.001). Regarding time spent at ordinary work; the HX08 group worked significantly less than the NoHX group (p=0.001). The HX08 group spent significantly more time cooking, cleaning and doing laundry than the NoHX group. The HX08 group smoked significantly more cigarettes than those in the HX9508 and NoHX groups (p=0.023 and 0.012 respectively).

Among the respondents 487/1323 (36.8%) used moisturisers daily. The HX9508 group used moisturisers significantly more than the other groups, 71.1%, followed by the HX08 group, 54.8%, the HX95group, 45.7% and the NoHX group, 30.6%, (p<0.001). Among females 52.7% (n=746), used moisturisers every day; 79% in the HX9508 group, 61.3% in the HX08 group, 56.2% in the HX95 group and 47.4% in the NoHX group (p<0.001). Among males 16.3% used moisturisers daily: 47.6% in the HX9508 group, 38.6% in the HX08 group, 22.7% in the HX95 group and 12.7% in the NoHX group (p<0.001). Males with hand eczema used moisturisers as often as women without hand eczema.

Factors predicting hand eczema

The analysis of endogenous and exogenous factors was performed with multinominal logistic regression. The results are shown in Table 4. Having had childhood eczema was the most significant predictor for one-year prevalence of hand eczema 2008 with odds ratios of 13.17 in the group HX9508 and 5.17 in the group HX08 compared to the group NoHX. The frequency of daily hand washing was significantly associated with the one-year prevalence of hand eczema only in the HX08 group. The daily usage of moisturisers was significantly associated with one-year prevalence of hand eczema in the groups HX9508 and HX08. High odds ratios, 1.40, for predicting one-year prevalence of hand eczema was found for female gender in the group HX9508. In the group HX08 the higher odds ratio for females was 1.19. However, none of these differences were significant.

DISCUSSION

In this study comprising 1,516 young adults, the one-year prevalence of hand eczema was more than 15%. One third of these individuals also had one-year prevalence at the baseline 1995. The one-year prevalence, and not the point prevalence, was used in all calculations because it better reflects the persistency, the relapsing course and the seasonal variations of the disease.[2,19] The increase in the one-year prevalence between the two occasions is in accordance with previous large Swedish cross-sectional studies with respect to the age groups.[3-5,22]

The estimated incidence of hand

Table 2

Comparisons of exogenous factors between the group with a 1-year prevalence of hand eczema in 2008 (Group HX), and the group reporting never having had hand eczema (Group NoHX)

	Group HX Mean, Median, (Q1 – Q3)			Group NoHX Mean, Median, (Q1 – Q3)		
	Females	Males	Total	Females	Males	Total
Number of persons in the household, yourself included (n = 1254)	3.0, 3, (2 – 4) **a>, c>**	2.5, 2, (2 – 3)	2.8, 3, (2 – 4) **b>**	2.7, 3, (2 – 4) **c>**	2.4, 2, (1 – 3)	2.6, 2, (2 – 4)
Number of children below 4 years of age (n = 1191)	0.8, 1, (0 – 1) **c>**	0.5, 0, (0 – 1)	0.7, 1, (0 – 1)	0.7, 0, (0 – 1) **c>**	0.6, 0, (0 – 1)	0.6, 0, (0 – 1)
Hours a day taking care of children 0 – 4 y (n = 1165)	5.3, 3, (0 – 8) **c>**	1.6, 0, (0 – 3)	4.3, 1, (0 – 6) **b>**	5.1, 0, (0 – 6) **c>**	2.0, 0, (0 – 3)	3.6, 0, (0 – 5)
Hours a day cooking (n = 1245)	1.3, 1, (1 – 1.5) **c>**	1.2, 1, (1 – 1)	1.2, 1, (1 – 1) **b>**	1.3, 1, (1 – 1.5) **c>**	1.0, 1, (0.5 – 1)	1.1, 1, (1 – 1)
Hours a day cleaning/making laundry (n = 1236)	1.3, 1, (1 – 2) **a>, c>**	0.7, 1, (0.3 – 1)	1.2, 1, (1 –1) **b>**	1.1, 1, (1 – 1) **c>**	0.7, 1, (0.2 – 1)	0.9, 1, (0.5 – 1)
Number of times a day washing hands at home (n = 1241)	8.8, 7, (5 – 10) **a>, c>**	4.4, 3.5, (3 - 5)	7.6, 6, (4 – 10) **b>**	7.2, 5, (4 – 10) **c>**	4.4, 4, (3 – 5)	5.9, 5, (3 – 7)
Number of times a day washing hands at work (n = 1193)	9.2, 6, (4 – 10) **a>, c>**	6.2, 3.5, (3 - 8) **a>**	8.3, 5, (3 – 10) **b>**	7.5, 5, (3 – 10) **c>**	4.5, 3, (2 – 5)	6.0, 4, (3 – 6)
Number of times a day washing hands, at home and at work (n = 1189)	17.4, 13.3, (10–20)**a>, c>**	10.6, 8 (5.8 - 14)	15.4, 12, (8 –17.8) **b>**	14.5, 11, (8 – 15) **c>**	8.8, 7 (5 – 10)	11.7, 9, (6 – 14)
If smoking; number of cigarettes a day (n = 112)	9.6, 8, (3.5 – 15)	7.3, 5, (2 – 15)	9.3, 8,(3.3 – 15)	6.5, 5, (2 - 10)	7.6, 5.5, (2 – 11.5)	7.1, 5, (2 – 10)
If using protective gloves at work: hours a day using them (n = 398)	2.8, 2, (1 – 3) **c<**	3.5, 3, (1.5 – 5.5)	2.9, 2, (1 – 4)	2.3, 2, (1 - 3)	3.8, 2, (1 – 6)	3.1, 2, (1 – 4)
Number of working hours at ordinary work (n = 1212)	35.6, 40, (30 – 40) **c<**	41.7, 40, (40 – 45)	37.3, 40, (34 – 40) **b<**	36.7, 40, (34 - 40)	41.9, 40, (40 – 45)	39.2, 40, (38 – 40)
Number of working hours at additional work (n = 107)	4.7, 3, (2 – 7.3)	11.2, 12.5(1.5 -20)	6.1, 3.5, (2 – 8)	10.4, 5, (2 – 12)	9.0, 6, (3 – 10)	9.6, 5, (3 – 10)
Number of working hours at ordinary and additional work (n = 101)	39.8, 41, (30 – 48) **c<**	51.0, 56,(41–59)	42.0, 42.5,(31-51)	44.3, 43 (39 – 50)	50.6, 50, (44 – 55)	47.9, 46, (41 – 53)
Hours a week gardening (during summer season). (n = 1201)	2.3, 1, (0 – 3)	2.5, 1, (0 – 3)	2.4, 1, (0 – 3)	2.5, 1, (0 – 3)	2.7, 1, (0 – 3)	2.6, 1, (0 – 3)
Hours a week repairing cars/engines (n = 1168)	0.2, 0, (0 – 0) **c<**	2.9, 0, (0 – 1)	1.0, 0, (0 – 0)	0.1, 0, (0 – 0)	1.5, 0, (0 – 1)	0.8, 0, (0 – 0)
Hours a week doing building work, restoration (n = 1179)	2.4, 0, (0 – 1) **c<**	3.6, 1, (0 – 3)	2.7, 0, (0 – 2)	2.4, 0, (0 – 1) **c<**	5.1, 1, (0 – 4.75)	3.8, 0, (0 – 2)
Hours a week doing sports/athletics (n = 1184)	4.4, 2, (1 – 4)	3.3, 2, (1 – 4)	4.1, 2, (1 – 4)	4.0, 2, (1 – 5)	4.2, 2, (1 – 4)	4.1, 2, (1 – 4)
Hours a week doing hobbies (n = 979)	4.3, 2, (0 – 5) **c<**	4.6, 2, (0 – 4.5)	4.4, 2, (0 – 5)	3.4, 2, (0 – 4.5)	5.2, 2, (0 – 5)	4.3, 2, (0 – 5)

Significant differences ($p<0.05$) between groups, totals and/or genders are **marked with bold letters. a:** significant differences within females or within males in different groups, **b:** significant difference between totals, **c:** significant difference between females and males in a group, **<** or **>:** the group or the gender has significantly lower or significantly higher frequency than the compared group. Mann-Whitney U test.

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eczema in our study was 11.6 cases per 1,000 person-years, 14.3 among females and 5.2 among males. Our figures are in the upper amplitude compared to an earlier population based study from Sweden, which showed between 11.4 and 3.7 cases/1,000 person-years among 20 to 29 year-old females and males, respectively.[23] One explanation could be that our study is prospective, and underreporting is to be expected in retrospective questionnaire studies.[24] Based on seven European hand eczema studies performed among 16 to 77 years-olds, the median incidence rate of hand eczema was 9.6 cases/1,000 person-years (range 4.6– 11.4) among women and 4.0 cases/1,000 person-years (range 1.4– 7.4) among men,[1] which is also slightly lower than our current findings, probably due to age-differences. To the best of our knowledge there are no comparable studies of the cumulative incidence in this age group. The cumulative incidence of hand eczema in our study across 13 years was 15.1% (18.6% for females and 10.7% for males). This can be considered to be a high proportion.[15] When using a questionnaire for estimating the true occurrence of a disease it is important to know the sensitivity and specificity of the question used. The question on one-year prevalence of hand eczema underestimates the occurrence.[25] However, regarding childhood eczema the occurrence has been found to be overestimated especially if the true prevalence is low.[5,19] Based on prevalence as well as incidence, the occurrence of hand eczema is approximately twice as common among females compared to men, which is similar to other population-based studies.[1,26,27]

The advantage of a longitudinal cohort study compared with a cross-sectional study is that it enables the estimation of both cumulative incidence and incidence rate. Another advantage of performing a follow-up study is the possibility to compare the development of hand eczema over time in relation to different risk factors.

The four groups (HX9508, HX95, HX08 and NoHX) were used to investigate the relationship between childhood eczema and the incidence of hand eczema. The assumption was that a smaller proportion of individuals who had hand eczema in 2008 but not in 1995 reported childhood eczema. However, there were no significant differences between the three hand eczema groups concerning childhood eczema. Furthermore, it was found that a higher proportion of individuals who had hand eczema at both occasions reported childhood eczema.

Thus, in this cohort childhood eczema was the most important predicting factor regardless of the debut of hand eczema. In 2008, around 30% of our sample reported childhood eczema (females 36%, males 20%). In a large population-based Swedish study performed from 2002 to 2003, among 21 to 30 year-olds, childhood eczema was reported by 30.1% of females and 20.8% of males.[4,28,29] The corresponding figures in the 31 to 40 year-olds were 21.8% and 16.2%.[30] Thus, in our study, the prevalence of childhood eczema was higher. Similar to other

Table 3

Comparisons of exogenous factors between the group HX9508, i.e. having had 1-year prevalence of hand eczema 1995 and 2008, the group HX95, i. e. having had hand eczema only 1995, the group HX08, i.e. having eczema only 2008 and the group NoHX, i. e. the group reporting never having had hand eczema

	HX9508 Mean (Q1-Q3)			HX95 Mean (Q1-Q3)			HX08 Mean (Q1-Q3)			NoHX Mean (Q1-Q3)		
	Females	**Males**	**Total**	**Females**	**Males**	**Total**	**Females**	**Males**	**Total**	**Females**	**Males**	**Total**
Number of persons in the household, yourself included (n = 1324)	2.9 (2-4)	2.5 (1-3)	2.8 (2-4)	2.9 (2-4)	2.6 (2-4)	2.8 (2-4)	3.0 (2-4) **a>, c>**	2.4 (2-3)	2.9 (2-4) **b>**	2.7 (2-4) **a<, c<**	2.4 (1-3)	2.6 (2-4) **b<**
Number of children below 4 years of age (n = 1259)	0.8 (0-1)	0.7 (0-1)	0.7 (0-1)	0.6 (0-1)	0.5 (0-1)	0.6 (0-1)	0.8 (0-1) **a>**	0.5 (0-1)	0.7 (0-1)	0.7 (0-1) **a<**	0.6 (0-1)	0.6 (0-1)
Hours a day taking care of children 0 – 4 years of age (n = 1234)	4.9 (0-8) **a<**	1.9 (0-3)	4.2 (0-6)	5.8 (0-8) **a>**	1.0 (0-1.5)	4.3 (0-5)	5.5 (0-8) **a>**	1.5 (0-2)	4.4 (0-6.3)	5.1 (0-6) **a>**	2.0 (0-3)	3.6 (0-5)
Hours a day cooking (n = 1314)	1.2 (1-1.3)	1.2 (1-1)	1.2 (1-1)	1.3 (1-2) **c>**	0.9 (0.5-1)	1.2 (1-1)	1.3 (1-2) **c>**	1.2 (0.8-1)	1.3 (1-1.3) **b>**	1.3 (1-1.5) **c>**	1.0 (0.5-1)	1.1 (1-1) **b<**
Hours a day cleaning/making laundry (n = 1304)	1.3 (1-1.6) **c>**	0.8 (0.3-1)	1.2 (1-1) **b>**	1.1 (1-1) **c>**	0.7 (0.4-1)	1.0 (1-1)	1.3 (1-2) **a>, c>**	0.7 (0.4-1)	1.2 (1-1) **b>**	1.1 (1-1) **a<, c>**	0.7 (0.2-1)	0.9 (0,5-1) **b<**
Number of times a day washing hands at home (n = 1309)	7.8 (4-10) **c>**	3.8 (2-5)	6.8 (3-10)	6.3 (5-8) **a<, c>**	5.0 (3-5.3)	5.9 (4-8) **b<**	9.3 (5-10) **a>, c>**	4.7 (3-5)	8.0 (4-10) **b>**	7.2 (4-10) **a<, c>**	4.4 (3-5)	5.9 (3-7) **b<**
Number of times a day washing hands at work (n = 1260)	8.3 (4-10) **c>**	5.2 (2.5-4)	7.4 (3 – 10) **b>**	7.6 (3.5-11) **c>**	4.3 (3-4)	6.5 (3-8)	9.7 (4-10) **a>, c>**	6.6 (3-10) **a>**	8.7 (3-10) **b>**	7.5 (3-10) **a > c<**	4.5 (2-5) **a<**	6.0 (3-6) **b<**
Number of times a day washing hands, at home and at work (n = 1255)	14.9 (9-17) **c>**	9.0 (5-11.5)	13.3 (7-16)	14.0 (9-19.5) **c>**	9.3 (6.8-10)	12.4 (8-16) **b<**	18.7 (10-21.5) **a>, c>**	11.3 (6-15) **a>**	16.5 (8-20) **b<**	14.5 (8-16) **a > c<**	8.8 (5-10) **a>**	11.7 (6-14) **b<**
If smoking; number of cigarettes a day (n = 112)	7.5 (5.8.7.8)	3.5 (2-5)	6.7 (2.9.7.3) **b<**	8.1 (5-11.8)	1 (1.0)	7.7 (4.5–10.5)	10.9 (6-15) **a>**	15 (1.0)	11.1 (7-15) **b>**	6.5 (2-10) **a<**	7.6 (2-11.5)	7.1 (2-10) **b<**
If using protective gloves at work: hours a day using them (n = 398)	2.8 (13-.5)	3.9 (2-5.8)	3.1 (1.5-4.5) **b>**	1.6 (1-2)	2.4 (0.5-4.5)	1.8 (1 – 2.8) **b<**	2.8 (1-3)	3.2 (1-5.5)	2.9 (1-3.3)	2.3 (1-3) **c<**	3.8 (1-6)	3.1 (1-4)
Number of working hours at ordinary work (n = 1279)	38.3 (35 – 40.5) **a>**	41.7 (40-44)	39.2 (38-42) **b>**	35.5 (32-40) **c<**	44.7 (40-50)	38.5 (36 – 45)	34.1 (30-40) **a<, c<**	41.8 (40-45)	36.3 (30-40) **b<**	36.7 (32-40) **a>, c<**	41.9 (40-45)	39.2 (38-40) **b>**
Number of working hours at ordinary and additional work (n = 107)	42.7 (32-49)	57.0 (57.0)	44.1 (33-51.8)	33.5 (29-38)	49.5 (45-54.5)	44.2 (35.8,51.5)	37.7 (29.3,47.3)	49.5 (39-59)	40.7 (30.5,51.8)	44.3 (38.5,49.5) **c<**	50.6 (44-55)	47.9 (41-53)
Hours a week gardening (n = 1270)	2.1 (0-3)	1.9 (0-3.5)	2.1 (0-3)	3.5 (0-3)	1.4 (0-2)	2.8 (0 – 2.5)	2.4 (0-2.3)	2.8 (0-3)	2.5 (0-2.5)	2.5 (0-3)	2.7 (0-3)	2.6 (0-3)
Hours a week repairing cars/engines (n = 1236)	0.2 (0-0)**<**	3.6 (0-1)	1.0 (0 -0)	0.1 (0-0) **c<**	0.5 (0-1)	0.2 (0-0)	0.3 (0-0) **c<**	2.6 (0-1)	1.0 (0-0)	0.1 (0-0) **c<**	1.5 (0-1)	0.8 (0-0)
Hours a week doing building work, restoration (n = 1245)	1.7 (0-2) **c<**	4.2 (0.6-5)	2.3 (0-2)	1.1 (0-1.5)	3.1 (0-3.5)	1.7 (0-2)	2.8 (0-1)	3.3 (0-2)	2.9 (0-1.5)	2.4 (0-1) **c<**	5.1 (0-4.8)	3.8 (0-2)
Hours a week doing sports (n = 1251)	4.2 (1-4)	2.7 (1-3.7)	3.8 (1-4)	2.5 (1-4)	2.7 (1-3.3)	2.6 (1-4)	4.5 (1-4.8)	3.6 (0.5-4)	4.2 (1-4)	4.0 (1-5)	4.2 (1-4)	4.1 (1-4)
Hours a week doing hobbies (n = 1035)	4.7 (2-5)	3.4 (0-6)	4.4 (2-5)	3.2 (0-4.8)	1.8 (0-3)	2.7 (0-4)	4.0 (0-4)	5.0 (0-4)	4.3 (0-4)	3.4 (0-4.5) **c<**	5.2 (0-5)	4.3 (0-5)

Significant differences ($p<0.05$) between groups, totals and/or genders are **marked with bold letters. a:** significant differences within females or within males in different groups, **b:** significant difference between totals, **c:** significant difference between females and males in a group, **<** or **>:** the group or the gender has significantly lower or significantly higher frequency than the compared group. Kruskal-Wallis Test and Mann-Whitney U test.

Table 4

Endogenous and exogenous factors associated with hand eczema analysed with logistic multinominal regression method, Group NoHX: never having had hand eczema, Group HX9508: having hand eczema 1995 as well as 2008, Group HX95: having had hand eczema only 1995 and Group HX08: having hand eczema only 2008

Group	Group HX9508 vs Group NoHX (N = 852)		Group HX95 vs Group NoHX (N = 836)		Group HX08 vs Group NoHX (N = 895)	
	Odds-ratio	95% CI for OR (p-value)	Odds-ratio	95% CI for OR (p-value)	Odds-ratio	95% CI for OR (p-value)
Having had childhood eczema	**13.17**	**6.74 – 25.72 (<0.001)**	**4.12**	**2.31 – 7.33 (<0.001)**	**5.17**	**3.33 – 8.03 (<0.001)**
Having had asthma	1.89	0.99 – 3.62 (0.54)	0.81	0.34 – 1.89 (0.619)	1.12	0.64 – 1.94 (0.699)
Having had rhino-conjunctivitis	1.64	0.86 – 3.10 (0.132)	0.98	0.53 – 1.81 (0.945)	1.51	0.95 – 2.40 (0.084)
Female gender	1.40	0.71 – 2.75 (0.334)	1.42	0.73 – 2.79 (0.304)	1.19	0.72 – 1.97 (0.500)
Number of times a day washing hands, at home and at work	0.99	0.97 – 1.02 (0.696)	1.00	0.97 – 1.03 (0.858)	**1.02**	**1.01 – 1.04 (0.038)**
Usage of moisturisers: daily vs less than daily	**5.17**	**2.82 – 9.51 (<0.001)**	1.49	0.81 – 2.73 (0.199)	**2.11**	**1.34 – 3.30 (0.001)**
Cooking:hours a day	1.00	0.69 – 1.43 (0.987)	1.00	0.66 – 1.51 (0.997)	1.10	0.87 – 1.37 (0.433)
Washing and cleaning: hours a day	1.19	0.81 – 1.77 (0.377)	0.81	0.48 – 1.39 (0.446)	1.23	0.94 – 1.60 (0.126)
Taking care of children < 4 years old: hours a day	1.01	0.97 – 1.06 (0.616)	1.02	0.98 – 1.07 (0.321)	0.99	0.96 – 1.03 (0.707)

Odds-ratios (OR) in predicting 1-year prevalence of hand eczema 2008 compared to the group NoHX, group HX9508 compared to group NoHX, and group HX08 compared to group NoHX. Confidence intervals (CI), 95%, and p-values are given for all variables. **Significant OR, CI and p-values are in bold text.**

studies, the relationship between having had hand eczema and reporting childhood eczema was highly significant.[31] The agreement in self-reports of childhood eczema at the two occasions was high. This high reliability over time in this age-group can be useful to know when hand eczema is diagnosed. However, the lower rate of reported childhood eczema in 2008 can be explained by recall bias as was found in a study comprising respondents aged 31 to 42 years.[32] For the individuals who reported only rhino-conjunctivitis, there was no significant association with one-year prevalence of hand eczema. Also, there was no association with asthma only, but there were very few respondents. Thus in our study no additional information concerning risk for hand eczema was obtained by asking about asthma or rhino-conjunctivitis. These results are in accordance with Meding et al. who showed that asthma and rhino-conjuntivitis in adults were only associated with hand eczema at an age below 30 years;[23] in another study, including adolescents, a marginally significant association with inhalant allergy was found.[33]

Analyses of exogenous factors showed that the individuals with hand eczema only in 2008, reported a significantly higher frequency of hand washing compared to the individuals without hand eczema.

Females with hand eczema spent significantly more time doing household activities than men with hand eczema (Table 3). Hand washing was more frequent among females with hand eczema than females without hand eczema as well as compared with men with hand eczema. In the multinominal regression analyses hand washing in the group HX08 was the only significant exogenous risk factor associated with hand eczema. In the majority of hand eczema studies hand washing is found to be the most significant risk factor for developing hand eczema.[34] In our cohort, other exogenous risk factors such as cooking, washing and cleaning and taking care of young children did not have any significant association with hand eczema. Furthermore, female gender was not a significant risk factor. However, it is well known that females have hand eczema more often than men. This can be explained by the high exposure to water and other skin irritants. Experimental as well as epidemiological studies[14,35] have demonstrated that female skin is not more sensitive to irritants than male skin[35] which is in line with our findings.

An interesting finding was the high odds-ratio in daily use of moisturisers in the two groups with current one-year prevalence of hand eczema (HX9508 and HX08). This pattern was not seen in the group having had hand eczema in 1995 (HX95).

When self-administrated questionnaires are used, it is important for the results to be adjusted based on sensitivity and specificity of validated questions. This is especially important in diseases that are common and affect the general health and well-being of individuals, such as hand eczema. The development of specific instruments like questionnaires implicates problems. In this case the questions regarding childhood and hand eczema were not validated in 1995 but 2,535 of the 2,572 pupils (98.6%) were clinically examined, and the sensitivity of 73% and the specificity of 99% were found.[15] The question regarding the one-year prevalence of hand eczema, which was used in the present study and in the first study, was previously validated.[19] Thus, the true one-year prevalence of hand eczema can be estimated from our data and is 20.6% for all; 26.8% among females and 12.5% among males.

The answers to the open questions on occupation as well as work tasks gave no further information regarding risk factors for developing or maintaining hand eczema. This circumstance seems to be a common problem in questionnaire studies.[3] In a study regarding occupational exposure to water as a risk factor for hand eczema, it was found that the title of an occupation gave misclassified results; exposure time and frequency of water use were more appropriate measures.[36] For result validity, it is important to have high response rates in general population studies.[37-39] The response rate in this study was almost two thirds of the individuals who received a questionnaire in the mail. Females were significantly more willing to participate than the males. There were, however, no significant differences within the female or the male groups regarding having had one-year prevalence of hand eczema at the two occasions. The response rate was similar to the annual national public health questionnaire performed by Swedish National Institute of Public Health.[40]

CONCLUSIONS

This study demonstrated that incidence of hand eczema in early adulthood tends to be associated with factors in everyday life such as frequent hand-washing. Regarding childhood eczema, the odds ratio for having hand eczema was twice as high in the HX9508 group compared to the group HX08, indicating a high vulnerability in this group. Furthermore, early onset of hand eczema seemed to be related to endogenous risk factors such as a history of childhood eczema. The higher frequency of hand eczema among women depended on exogenous factors.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

The authors together designed the study, analysed the data and wrote the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Thyssen JP, Johansen JD, Linneberg A, Menné T: The epidemiology of hand eczema in the general population – prevalence and main findings. *Contact Dermatitis* 2010; 62:75-87.
2. Meding B: Epidemiology of hand eczema in an industrial city. *Acta Derm Venereol* 1990; 153(Suppl):1-43.
3. Montnemery P, Nihlen U, Lofdahl CG, Nyberg P, Svensson A: Prevalence of hand eczema in an adult Swedish population and the relationship to risk occupation and smoking. *Acta Derm Venereol* 2005; 85:429-432.
4. Meding B, Jarvholm B: Hand eczema in Swedish adults—changes in prevalence between 1983 and 1996. *J Invest Dermatol* 2002; 118:719-723.
5. Stenberg B, Meding B, Svensson A: Dermatology in public health - a model for surveillance of common skin diseases. *Scandinavian J Public*

Health 2010; 38:368-374.
6. Bingefors K, Lindberg M, Isacson D: Quality of life, use of topical medications and socio-economic data in hand eczema: a Swedish nationwide survey. *Acta Derm Venereol* 2011; 91:452-458.
7. Flyvholm M, Bach B, Rose M, Frydendall Jepsen K: Self-reported hand eczema in a hospital population. *Contact Dermatitis* 2007; 57:110-115.
8. Van der Meer EW, Boot CR, Jungbauer FH, van der Klink JJ, Rustemeyer T, Coenraads PJ, van der Gulden JW, Anema JR: Hands4U: a multifaceted strategy to implement guideline-based recommendations to prevent hand eczema in health care workers: design of a randomised control trial and (cost) effectiveness evaluation. *BMC Public Health* 2011; 11:669.
9. Augustin M: Versorgungsforschung in der Dermatologie. *Hautarzt* 2011; 62:168-169.
10. Meding B, Wrangsjö K, Järvholm B: Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 2005; 152:975-980.
11. Moberg C, Alderling M, Meding B: Hand eczema and quality of life: a population-based study. *Br J Dermatol* 2009; 161:397-403.
12. Dickel H, Kuss O, Schmidt A, Kretz J, Diepgen TL: Importance of irritant contact dermatitis in occupational skin disease. *Am J Clin Dermatol* 2002; 3:283-289.
13. Nielsen NH, Linneberg A, Menne T, Madsen F, Frolund L, Dirksen A, Jorgensen T: The association between contact allergy and hand eczema in two cross-sectional surveys 8 years apart. The Copenhagen allergy study. *Contact Dermatitis* 2002; 47:71-77.
14. Bryld LE, Hindsberger C, Kyvik KO, Agner T, Menne T: Risk factors influencing the development of hand eczema in a population-based twin sample. *Br J Dermatol* 2003; 149:1214-1220.
15. Yngveson M, Svensson A, Isacsson A: Evaluation of a selfreported questionnaire on hand dermatosis in secondary school children. *Acta Derm Venereol* 1997; 77:455-457.
16. Yngveson M, Svensson A, Isacsson A: Prevalence of self-reported hand dermatosis in upper secondary school pupils. *Acta Derm Venereol* 1998; 78:371-374.
17. Susitaival P, Kanerva L, Hannuksela M, Jolanki R, Estlander T: *Touhilampi Questionnaire for Epidemiological Studies of Contact Dermatitis and Atopy*. Helsinki: Finnish Institute of Occupational Health; 1996. [People and Work. Research Report 10].
18. Susitaival P, Flyvholm MA, Meding B, Kanerva L, Lindberg M, Svensson A, Olufsson JH: Nordic occupational skin questionnaire (NOSQ-2002): a new tool for surveying occupational skin diseases and exposure. *Contact Dermatitis* 2003; 49:70-76.
19. Meding B, Barregå rd L: Validity of self-reports of hand eczema. *Contact Dermatitis* 2001; 45:99-103.
20. Anveden I, Lidé n C, Alderling M, Meding B: Self-reported skin exposure—validation of questions by observation. *Contact Dermatitis* 2006; 55:186-191.
21. Ahlbom A, Norell S: *Introduction to Modern Epidemiology*. Chestnut Hill: Epidemiology Resources Inc.; 1990::25-26.
22. Meding B, Lidé n C, Berglind N: Self-diagnosed dermatitis in adults. Results from a population survey in Stockholm. *Contact Dermatitis* 2001; 45:341-345.
23. Meding B, Järvholm B: Incidence of hand eczema-a population-based retrospective study. *J Invest Dermatol* 2004; 122:873-877.
24. Bregnhøj A, Søsted H, Menné T, Johansen Duus J: Validation of self-reporting of hand eczema among Danish hairdressing apprentices. *Contact Dermatitis* 2011; 65:146-150.
25. Stenberg B, Lindberg M, Meding B, Svensson Å : Is the question " Have you had childhood eczema?" useful for assessing childhood atopic eczema in adult population surveys? *Contact Dermatitis* 2006; 54:334-337.
26. Yngveson M, Svensson A, Johannisson A, Isacsson A: Hand dermatosis in upper secondary school pupils: 2-year comparison and follow-up. *Br J Dermatol* 2000; 142:485-489.
27. Meding B: Differences between the sexes with regard to work-related skin disease. *Contact Dermatitis* 2000; 43:65.
28. Rystedt I: Hand eczema and long-term prognosis in atopic dermatitis. *Acta Derm Venereol* 1985; 117:1-59.
29. Nilsson E: Individual and environmental risk factors for hand eczema in hospital workers. *Acta Derm Venereol* 1986; 128(Suppl):1-63.
30. Röhrl K, Stenberg B: Lifestyle factors and hand eczema in a Swedish adolescent population. *Contact Dermatitis* 2010; 62:170-176.
31. Nyré n M, Lindberg M, Stenberg B, Svensson M, Svensson Å , Meding B: Influence of childhood atopic dermatitis on future worklife. *Scand J Work Environ Health* 2005; 31:474-478.
32. Moberg C, Meding B, Stenberg B, Svensson A, Lindberg M: Remembering childhood atopic dermatitis as an adult: factors that influence recollection. *Br J Dermatol* 2006; 155:557-560.
33. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE: Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense adolescence cohort study on atopic diseases and dermatitis. *Br J Dermatol* 2001; 144:523-532.
34. Anveden I, Wrangsjö K, Järvholm B, Meding B: Self-reported skin exposure—a population-based study. *Contact Dermatitis* 2006; 54:272-277.
35. Agner T: Noninvasive measuring methods for the investigation of irritant patch test reactions; a study of patients with hand eczema, atopic dermatitis and controls. *Acta Derm Venereol* 1992; 173(Suppl):1-26.
36. Anveden Berglind I, Alderling M, Järvholm B, Lidé n C, Meding B: Occupational skin exposure to water: a population-based study. *Br J Dermatol* 2009; 160:616-621.
37. Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, Cooper R, Felix LM, Pratap S: Methods to increase response to postal and electronic questionnaires (Review). *Cochrane Database Syst Rev* 2009, (3):MR000008. 10.1002/14651858.MR000008.pub4.
38. Data quality for the 2006 survey of labour and income dynamics (SLID) http://www.statcan.gc.ca/pub/75f0002m/2008005/section5-eng.htm
39. Tolonen H, Helakorpi S, Talala K, Helasoja V, Martelin T, Prättäla R: 25-year trends and socio-demographic differences in response rates: Finnish adult health behaviour survey. *Eur J Epidemiol* 2006; 21:409-415.
40. Swedish National Institute of Public Healthhttp://www.fhi.se/Documents/Statistik-uppfoljning/Folkhalsoenkaten/vad_betyder_bortfallet100330.pdf.

Apps: *How do you know which ones to avoid?*

Continued from page 22

of marketing an anti-wrinkle cream.

"Another important thing to note is if the information from the source you are reading has references, such as citations . . . I think that makes it a stronger resource," she noted.

Be cautious if apps offer services

Dr. Brewer said to warn patients to be cautious about apps that appear to offer a service.

"Last year there were two apps that were removed from the market, which were essentially apps that claimed to treat acne using the built-in camera light on your phone as a strobe light, but there have not been studies done on it," said Dr. Brewer.

Dr. Ann Chang Brewer

Dr. Adam Mamelak

Apps are suspect if, for instance, they claim to analyse a mole by taking a photo of it and examine it using the app or possibly by sending the photo to a physician to determine if it is cancerous or not, according to Dr. Brewer.

She said apps from a trusted source, that permit patients to take photographs and document a mole over time can be useful as long as the process is guided by a physician.

"I think it should be used as an adjunct to the care that [a patient] is already receiving by their primary doctor or dermatologist or nurse practitioner," she said. "Those are helpful because when the dermatologist sees [the patient] they can compare the skin lesion to a previous picture from two years ago and that can be very helpful."

Dr. Adam Mamelak, a Canadian and U.S. board-certified dermatologist and founder of the Sanova Dermatology in Austin, Tex., told THE CHRONICLE OF SKIN & ALLERGY that apps that survey moles are risky and ambiguous.

"I have had a patient that submitted [a photo of a mole] and, rightfully so, the app told him that he should go seek a dermatology evaluation so he came to me. That's a good thing," Dr. Mamelak said.

"But, some of the applications are not so black and white. They will categorize the risk as mild, moderate, or severe.

"If you take a picture of a mole and you submit it and it comes back as a severe concern, you are going to seek medical help right away. If you get it back as a mild one, you will say 'it is probably fine; it is nothing to worry about.' But, what if it is a moderate concern, what does that mean?"

Apps should not replace face-to-face interaction

Dr. Mamelak said the mole mapping apps can be useful, especially because cell phones have much higher quality cameras than they used to, which resulted in blurry images.

"As long as it is done with the involvement of a physician, I think it is great. If it is just done on their own, that is when I think the patient can get into trouble," said Dr. Mamelak.

"I don't think apps can replace face-to-face contact with a physician."

THERAPEUTIC INDEX

Cellulitis cases in Canada hospitalized more frequently

Continued from page 1

Investigators used The Canadian Discharge Abstract Database from 2004 to 2008 to review data of a total of 65,454 patients in Canada hospitalized for cellulitis. The average stay of these patients was seven days and extended stays greater than that were often associated with a consultation by a surgical or dermatology service.

The mortality rate was 1% and one factor associated with mortality included a surgical or infectious disease consult. The authors suggested this was an indicator of a more complicated disease such as necrotizing fasciitis.

Cellulitis over-diagnosed

"One issue [the study] highlights is the burden of disease that comes from cellulitis in Canada. I think the numbers are pretty impressive that over 65,000 patients over a five-year period were hospitalized with a primary diagnosis of cellulitis," said Dr. Aaron Drucker, a fifth year dermatology resident at the University of Toronto and one of the study's authors.

Dr. Aaron Drucker

Dr. Akerke Baibergenova

"Then there is the issue of misdiagnosis. We do not know for sure that any of these cases were misdiagnosed, but we do think—based on personal experience—that cellulitis is often over-diagnosed."

Dr. Akerke Baibergenova, a dermatologist at Bayview North Dermatology Clinic in Toronto and the study's lead investigator, said stasis dermatitis is often misdiagnosed as cellulitis. Dr. Baibergenova referenced a presentation given at the American Medical Information Association and The Agency of Healthcare Research and

Message from the Medical Editor

Continued from page 3

because of recently described comorbid disease, dermatologists are now actively collaborating with internal medicine, cardiology, endocrinology and psychiatry colleagues in addition to our rheumatology colleagues. For chronic spontaneous urticaria, with the introduction of omalizumab we are already seeing significant collaboration between dermatologists, allergists and immunologists, not only on the research front but in the development of Canadian-specific guidelines for the management of chronic spontaneous urticaria.

These types of collaborations are certainly not only very helpful for the patient but have enhanced the profile of dermatologists amongst our colleagues.

The second piece of Canadian research I would like to bring to your attention is that of Dr. Robert Bissonnette, who studied palmoplantar pustular psoriasis and palmoplantar pustulosis (see page 27). Although no therapeutic advancement was made by targeting IL-12/23 the fact that cytokine expression was studied and IL-17 showed increased expression, gives us hope that new therapies presently being studied for psoriasis may give us the opportunity to develop new therapies for this impactful and therapeutic challenging condition.

—Wayne P. Gulliver, MD, FRCPC
Medical Editor

Quality Diagnostic Error in Medicine National Conference on May 31, 2008, where researchers found that cellulitis is misdiagnosed in about 20% to 25% of all cases.

"[The importance of this study] is to raise the awareness of emergency medicine physicians as well as internal medicine physicians to be able to better differentiate between cellulitis [and] stasis dermatitis . . . We should alert them that these are quite common conditions and they are treated in very different ways," said Dr. Baibergenova.

Cellulitis is usually unilateral and painful whereas stasis dermatitis is bilateral and pruritic, according to Dr. Baibergenova. She said some internists and emergency medicine physicians do not have enough training in dermatology to be able to distinguish these two conditions.

Dr. Baibergenova said cellulitis is considered more dangerous than stasis dermatitis, which is why a round of antibiotics is often administered even though stasis dermatitis does not require this type of treatment.

Concerns with antibiotics

Dr. Drucker said physicians should not use the "better to be safe than sorry" approach that is often taken when treating cellulitis, because complications can arise from antibiotics, including negative reactions to certain drugs, antibiotic resistance, and clostridium difficile diarrhea.

"Cellulitis is over-diagnosed because you do not want to miss an infection that could be easily treated with antibiotics. But, what needs to happen is these patients need to be better diagnosed," said Dr. Drucker.

Dr. Drucker said he was not surprised to find longer stays being associated with dermatology consultation because it is a logical connection that it would be a more difficult case if the service was needed. However, he was surprised with the long hospital stays.

"A lot of the time cellulitis can be managed as an outpatient," said Dr. Drucker. "It is not that the patients should not go to the emergency room for it, but then often they can be sent home with the antibiotics, and then if they need intravenous antibiotics they can have that at home through CCAC [Community Care Access Centre]."

Dr. Drucker said a British study demonstrated improved rates of accurate cellulitis when a dermatology service was called in for every consultation. The dermatologist caught more misdiagnoses and patient care was improved (*Br J Dermatol* 2011; 164(6):1362-1328).

More consultation, training needed

"More should be done, whether it is making dermatology or infectious disease consultations more available, making infectious disease consult more available, or having some better training in place for primary care doctors to better recognize cellulitis, to prevent misdiagnosis in these patients, and to prevent the unnecessary use of antibiotics and unnecessary hospitalization," said Dr. Drucker.

He added that it is difficult to develop a uniform plan in Canada because the tertiary hospitals have greater access to consult services, whereas some peripheral hospitals might not have those resources available.

For more information, refer to: http://ow.ly/sSDi3

Research

T regs are stable in skin

■ Subset of regulatory T-cells identified in human skin

From the News Resources of The Chronicle

A subset of regulatory T cells (Tregs) has been identified in human skin which is stable and different from those Tregs found in blood, and there is evidence that these skin Tregs are qualitatively defective in inflammatory skin disease, according to research published in the *Journal of Clinical Investigation* (Mar. 3, 2014; 124(3):1027-1036).

Having previously discovered that almost all Tregs in normal murine skin had properties similar to memory cells, and remarking on the importance of these cells in regulating tissue inflammation in mice, the authors set out to analyse a similar cell population in humans. They discovered that almost all the Tregs in normal human skin had an activated memory phenotype (mTreg). As well, the cutaneous mTregs had different cell surface marker expression and cytokine production than mTregs previously identified in peripheral blood—approximately 5% of CD4+ T-cells in peripheral blood express the Foxp3 protein consistently, yet approximately 20% of adult skin-localized CD4+ T-cells express Foxp3. As well, little homology was seen in sequence comparison of TCRs between conventional memory T helper cells and mTregs isolated from skin, which the authors say suggests they recognize different antigens.

In adult skin, the majority of these mTreg cells were found near hair follicles, while regions of skin with high density of hair follicles—such as the face and scalp—also had a significantly higher percentage of Tregs compared to skin with low hair density. As well, the cells were non-migratory and relatively unresponsive in healthy skin, with the majority of skin cells isolated from human skin lacked expression of the chemokine receptor CCR7, which regulates memory T-cell migration. However, in samples of inflamed skin taken from psoriatic patients, researchers found increased percentages and absolute numbers of Foxp3-expressing T cells, and CD45RO+CD4+Foxp3+ cells in lesional skin were producing more interleukin (IL)-17. The mTregs were also highly proliferative in the lesional samples.

This suggests that excessive proliferation—possibly associated with effector cytokine production—is a property that mTregs possess in psoriasis and similar inflammatory skin conditions, the authors write, though they note that whether these Treg abnormalities cause or are caused by the inflammation remains to be clarified.

Research of Note

BULLOUS PEMPHIGOID PATIENTS COMPARED TO MALIGNANT CANCER COHORT

A nation-wide, record-linked study of U.K. National Health Service (NHS) hospital admission data and mortality statistics from 1999 to 2011 was conducted to evaluate the risk of concurrent or subsequent bullous pemphigoid (BP)—comparing a cohort of 2,873,720 individuals with malignant cancers to a reference cohort. Standardized rate ratios (RRs), based on person-years at risk, were calculated to compare the observed and expected numbers of BP cases in the cancer and reference cohorts. Members of the malignant cancer cohort were found to not be at overall greater risk of concurrent or subsequent BP than the cohort of those without a record of such cancer (RR 0.96, 95% CI 0.88-1.04), though there were elevated risks of BP seen in some sub-cohorts: those with kidney cancer, laryngeal cancer, and lymphoid leukemia. As well, a corresponding risk analysis of concurrent and subsequent malignant cancers in a cohort of people with a principal diagnosis of BP found no increased risk vs. the reference cohort (RR 1.00, 95% CI 0.92-1.09).

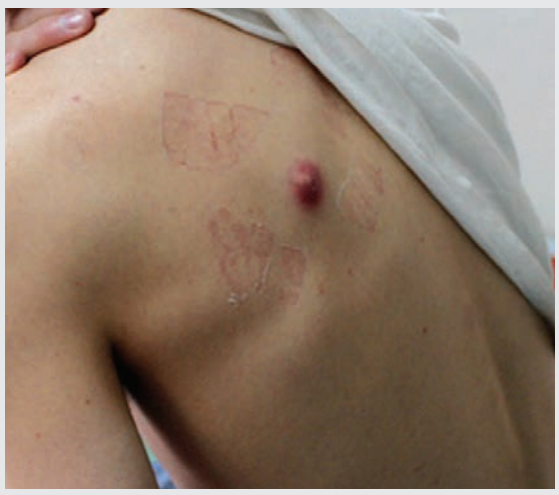
Ong E, Goldacre R, Hoang U, et al: Associations between bullous pemphigoid and primary malignant cancers: an English national record linkage study, 1999-2011, in *Archives of Dermatological Research* (Jan. 2014, 306(1):75-80).

EVALUATING EFFECTS OF COLD THERAPY ON SKIN BURNS

To evaluate the pathophysiological effects of cold therapy on microcirculation, edema formation, and histomorphology in superficial burns, 12 volunteers (eight females, four males, with an average age of 30.4±14.1 years) were given superficial burns on the backs of both hands. One of each pair of burns was untreated as a control, the other was treated by local cold application. Several parameters (epidermal thickness (ET), granular cell size (GCS), individual blood cell flow (IBCF) and functional capillary density (FCD)) were evaluated using intravitalmicroscopy prior to the burn (t0), immediately after the application of cold therapy (t1), and 15 minutes (t2) and 30 minutes (t3) after treatment. Both ET and GCS were observed to increase significantly in the control group, and slightly in the cold treatment group, at t1, though increases were insignificant from t2 onward. IBCF and FCD rose in the control group, but decreased in the cold treatment group at t1. The researchers conclude that while microcirculation, edema formation, and histomorphology of superficial burns are significantly influenced by immediate cold therapy, the changes are transient and become ineffective after 30 minutes.

Altintas B, Altintas AA, Kraemer R, et al: Acute effects of local cold therapy in superficial burns on pain, in vivo microcirculation, edema formation and histomorphology, in *Burns* (published in the Dec. 16, 2013 online edition).

Diagnostic Quiz



A. Sebaceous cyst
B. Neurofibroma
C. Lipoma

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Correct answer: Sebaceous cyst

What THE LAY PRESS *is saying about . . .*

EFFECTS OF PROTEIN INHIBITOR MAY LEAD TO NEW THERAPIES

Molecules in skin that contribute to both unwanted hair growth and alopecia have been identified by researchers from the University of Pennsylvania School of Medicine, potentially leading to treatments for these conditions, reports the **National Post** (Dec. 6, 2013).

The protein inhibitor Dkk1 was found to inhibit the intracellular Wnt/*b*-catenin pathway, which would result in baldness. Even after balding had begun, stem cells in the dormant follicles were maintained, and would re-activate and restore hair growth if Dkk1 was removed, according to the news outlet. The researchers also discovered that the Wnt/β-catenin pathway was also normally active in regions of skin that were normally hair-free, such as the palms of the hands, and between follicles. Senior author Sarah Millar, PhD, told the **Post:** "Our results suggest that therapeutics capable of decreasing levels of Wnt/β-catenin signalling in the skin could potentially be used to block growth of unwanted hair, and/or to treat certain skin tumours." She also suggeted that Wnt signalling-activating agents might be used to induce dormant follicles to grow hair in conditions such as male pattern baldness.

ACCURATE DX OF SKIN CANCER BY AMATEUR EVALUATORS?

While individual amateur evaluators are known to be poor at determining if a mole is cancerous or not, it appears that collectively, groups of such evaluators are significantly more accurate than individuals alone, reports **The Salt Lake Tribune** (Dec. 16, 2013).

Research from the University of Utah and Texas Tech University suggests that having a mole verified by hundreds of individuals could greatly improve the odds of accurate diagnosis. There is a shortage of dermatologists in the U.S., the news outlet reports, and the ABCDE method of self-examination is proving to be ineffective. "It takes quite a bit of skill to look at a lesion and determine whether it is cancerous or not," Jakob Jensen, one of the study's authors and an assistant communications professor at the university told the news outlet. The researchers showed high-resolution images of 40 moles—nine previously diagnosed as melanoma—to 500 adults, and asked them to circle those they considered suspicious. Individual participants accurately identified the melanomas only 50% of the time, yet 19% of participants were correct 90% of the time.

BANNED INGREDIENT SHOWN TO CAUSE CONTACT DERMATITS

Cosmetics Europe, the European cosmetics trade association, has instructed its members to stop using the preservative methylisothiazolinone (MI) because it has been associated with an increase in the prevalence of contact dermatitis, reports **The Telegraph** (Dec. 14, 2013).

Introduced in 2006, MI was used in a wide range of products from moisturizers to baby wipes. However, contact sensitivity to the chemical has become common, with dermatologists estimating that one in 10 patients presenting with eczema or contact dermatitis was allergic to the preservative. Only nickel more frequently causes reactions, the news outlet reports. MI had previously been used in combination with methylchloroisothiazolinone (MC), but ironically, concerns about MCI causing allergies led to MI being used alone at higher concentrations. In European regulations introduced in 2005, MI could be used on its own at concentrations up to 100 ppm. The **Telegraph** reports that dermatologists expect a rate of allergic reaction of 1 to 2% for a cosmetic product, but U.K. clinic data showed MI reaction rates as high as 10%.

NON-WHITE POPULATIONS HAVE LESS SKIN CANCER KNOWLEDGE

A recent study has revealed that members of non-Caucasian populations have less knowledge of skin cancer, reports **Reuters** (Jan. 3, 2013).

While melanoma is diagnosed in Hispanic, African-American and Asian individuals at a significantly lower rate than in those with Caucasian skin (between one and five in 100,000, compared to between 20 and 32 in 100,000), when they are diagnosed it tends to be not until the cancer has reached a more advanced stage, lowering their odds of survival, the news outlet reports. Researchers from the NYU Langone Medical Center surveyed 152 visitors to a dermatology clinic at a New York City public hospital. Knowledge of the ABCDE warning signs—asymmetry, border, colour, diameter, and evolution—was low in all respondents, but even lower among those without white skin. As well, the majority of participants incorrectly said that skin cancer screenings help prevent disease.

"Our study significantly adds to the field by defining clear gaps in patient knowledge about melanoma characteristics (ABCDE criteria) here in the United States," the study authors wrote.

Department Editor: John Evans

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[1] Data on file. Galderma Canada.

[2] Safety & Tolerability in Infants/Toddlers with Atopic Dermatitis, Study (Pediatric Dermatology Vol. 29 No.5 590-597, 2012)

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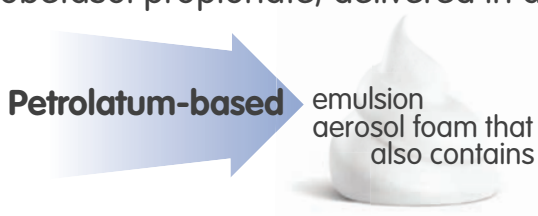

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Contraindications:

- Hypersensitivity to other corticosteroids
- Viral (e.g. herpes or varicella) lesions of the skin, bacterial or fungal skin infections, parasitic infections, skin manifestations relating to tuberculosis or syphilis, eruptions following vaccinations
- Treatment of rosacea, acne vulgaris, pruritus without inflammation, perianal and genital pruritus, perioral dermatitis, or infections of the scalp
- Topical application to the eye

Most serious warnings and precautions:

- **HPA axis suppression:** should not be used under occlusion, over extensive areas, or on the face, axillae, groin, scrotum or other intertriginous areas
- **Prior use of corticosteroids:** patients should inform physicians
- **Extremely flammable propellant:** avoid fire, open flame, spark or smoking during and immediately following application
- **Pediatric patients:** safety has not been studied in patients <6 years of age; not recommended in patients <12 years of age

Other relevant warnings and precautions:

- Caution in stasis dermatitis and other skin diseases with impaired circulation
- Use around chronic leg ulcers may be associated with higher occurrence of local hypersensitivity reactions and increased risk of local infection
- Systemic absorption may result in hypothalamic-pituitary-adrenal (HPA) axis suppression, glucocorticosteroid insufficiency, Cushing's syndrome, hyperglycemia and glucosuria
- Monitor for HPA-axis suppression in conditions which augment systemic absorption
- Pediatric patients may be more susceptible to systemic toxicity
- Risk of serious adverse events in patients with acute illness or injury: patients/caregivers should be instructed to use OLUX®-E Foam for the minimum amount of time necessary to achieve the desired results
- Increased risk of infections
- Caution on lesions close to the eye, risk of increased intraocular pressure, glaucoma or cataracts
- Local hypersensitivity reactions may resemble symptoms of the condition under treatment
- Risk of irritation, striae or atrophy of the skin or subcutaneous tissue; caution on lesions of the face, groin and axillae
- Should not be administered during pregnancy or lactation unless the expected benefits to the mother outweigh the potential risks to the fetus or the infant; if used during lactation, do not apply to the chest so as to avoid accidental ingestion by the infant
- Caution in elderly
- Minimum quantity/duration in elderly patients and patients with renal/hepatic impairment
- Caution in psoriasis

Dosage and method of administration:

- Apply a thin layer of OLUX®-E Foam to the affected area(s) twice daily, morning and evening for a maximum of 2 weeks and patients should not use greater than 50 grams per week.
- Dispense the smallest amount of foam necessary (up to a maximum of a golf-ball-size) to adequately cover the affected area(s) with a thin layer.
- Do not use on the eye, orally or intravaginally, or on other mucus membranes.

Adverse reactions:

- In a controlled clinical trial, the most frequently reported treatment-related adverse reactions with OLUX®-E Foam were application site reaction in 2%, application site atrophy in 2% and application site pigmentations changes (1%).

For more information:

Please consult the product monograph at http://webprod5.hc-sc.gc.ca/dpd-bdpp/ for important information relating to contraindications, warnings and precautions, adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The product monograph is also available by calling 1-800-387-7374.

* Comparative clinical significance has not been established.

† Double-blind study of 377 patients aged ≥12 years with moderate-to-severe atopic dermatitis. Patients were randomized to OLUX®-E Foam twice daily for 2 weeks or vehicle foam. Treatment success was defined as the proportion of patients who had all of the following: an Investigator's Static Global Assessment (ISGA) score of clear or almost clear, a minimum improvement in the 5 point ISGA score of 2 grades from baseline to Week 2, and a score of absent or minimal for both erythema and induration/papulation at Week 2. The majority of the subjects enrolled (87%, 328/377) had a baseline ISGA score of 3 and 12% (44/377) had a baseline ISGA score of 4. The mean extent of atopic dermatitis (% BSA) at baseline was 14.9% for the EF clobetasol foam group and 13.8% for the vehicle foam group.

‡ Clinical significance has not been established.

§ For a list of additional ingredients, please refer to the Product Monograph.

Reference: 1. OLUX®-E Foam Product Monograph. GlaxoSmithKline Inc., September 10, 2013.

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Delivered in VersaFoam® Emulsion

Pr Olux®-E (clobetasol propionate) Foam, 0.05%

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